STRUCTURAL VARIATIONS OF TRICYCLODECADIENONES IN SYNTHETIC PERSPECTIVE

J.H.M. Lange

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EEN WETENSCHAPPELIJKE PROEVE OP HET GEBIED VAN DE NATUURWETENSCHAPPEN IN HET BIJZONDER DE CHEMIE

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE KATHOLIEKE UNIVERSITEIT TE NIJMEGEN VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN IN HET OPENBAAR TE VERDEDIGEN OP DINSDAG 12 DECEMBER 1989, DES NAMIDDAGS TE 3.30 UUR

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Promotor: Prof. Dr. B. Zwanenburg

Co-promotor: Dr. A.J.H. Klunder

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Ter nagedachtenis aan mijn vader

Aan mijn moeder

Voor Jannet

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tekening voorpagina: Jannet Siccama

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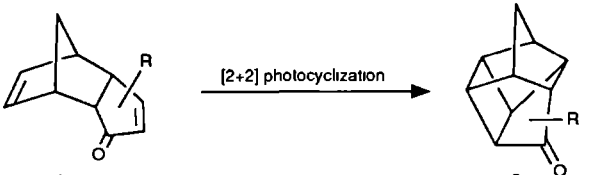
CHAPTER 1

INTRODUCTION

1.1 SYNTHESIS AND PROPERTIES OF TRICYCLO[5.2.1.0^{2,6}]DECADIENONES

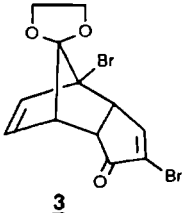
Rigid alicyclic compounds provide ideal systems for investigating interactions between nonbonded atoms and for studying stereochemical and mechanistic aspects of organic reactions. An intriguing part of alicyclic chemistry has been, and still is, the synthesis and study of highly strained polycyclic ring systems. The discovery of the intramolecular photochemical [2+2] cycloaddition reaction as a general method for the synthesis of highly strained cyclobutane containing cage-type polycycles, about three decades ago, constitutes an important landmark in organic alicyclic chemistry[1-4]. In the Department of Organic Chemistry of the Nijmegen University there is a continuing program on the synthesis of functionalized cubane and related cage compounds with the aim to establish the relationship between their chemical reactivity and their cage strain energy[5-8]. Particular attention has been devoted to the synthesis and chemical behavior of bridgehead cage alcohols and their derivatives.

Scheme 1



1 2

Key intermediates in the synthesis of these cage-type structures are appropriately functionalized *endo*-tricyclo[5.2.1.0^{2,6}]decadienones **1**, which, upon irradiation, readily undergo photocyclization to produce 1,3-bishomocubanones **2** (Scheme 1). Further modification of the cage compounds **2** is then accomplished either by cage contraction or by cage expansion. Examples of suitable tricyclic photoprecursors are dibromoketone **3**, enol acetate **4** and ester **5**. All these tricyclodecadienones are relatively easy to prepare in reasonable yields and quantities.



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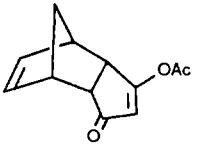

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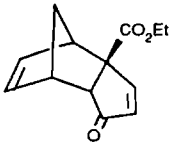

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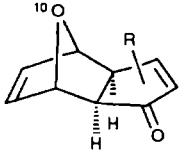
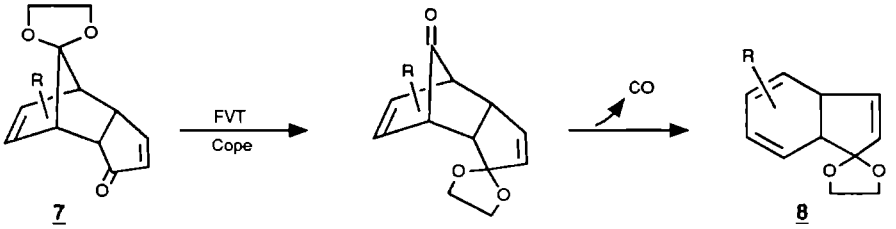


6

During this study of strained cage systems, it was realized that the tricyclo[5.2.1.0^{2,6}]decadienones **1** not only are valuable precursors for cage compounds but also offer interesting synthetic prospects in a more general sense. As was demonstrated by Cillissen[9] tricyclo[5.2.1.0^{2,6}]decadienones **7** serve as synthons for functionalized dihydroindenone ethylene acetals **8**. This thermal conversion involves a

Cope rearrangement and a subsequent extrusion of carbon monoxide, which could effectively be performed employing the technique of flash vacuum thermolysis (FVT) (Scheme 2).

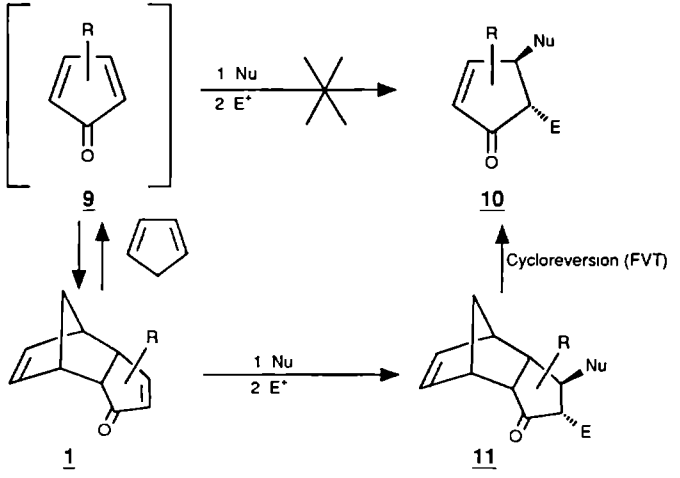
Scheme 2



7 **8**

The tricyclo[5.2.1.$0^{2,6}$]decadienone system **1** can serve as a synthetic equivalent of cyclopentadienone as it essentially is a cyclopentadienone **9** in which one of the two double bonds is masked in the crossed Diels-Alder adduct with cyclopentadiene (Scheme 3). The remaining enone can therefore be subjected to selective transformations, *e.g.* by nucleophilic addition, followed by electrophilic substitution, to form functionalized tricyclodecenones **11**. Subsequent thermal cycloreversion (retro Diels-Alder reaction) then regenerates the protected enone moiety to produce functionalized cyclopentenones **10**.

Scheme 3

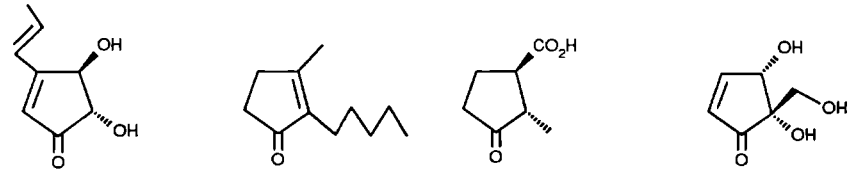


9 **10** **1** **11**

It was found that the technique of flash vacuum thermolysis[10] is most useful in effecting the thermal demasking process. The structurally related *exo*-10-oxatricyclo[5.2.1.$0^{2,6}$]decadienones **6** can also be utilized[11] as synthetic equivalents for cyclopentadienones **9**. It should be mentioned that cyclopentadienones **9** are generally extremely reactive[12,13]. They have a particular tendency to undergo rapid dimerization and are therefore not suited for the synthesis of cyclopentenones.

The synthetic strategy depicted in Scheme 3 is a very attractive one. As a consequence of the rigid

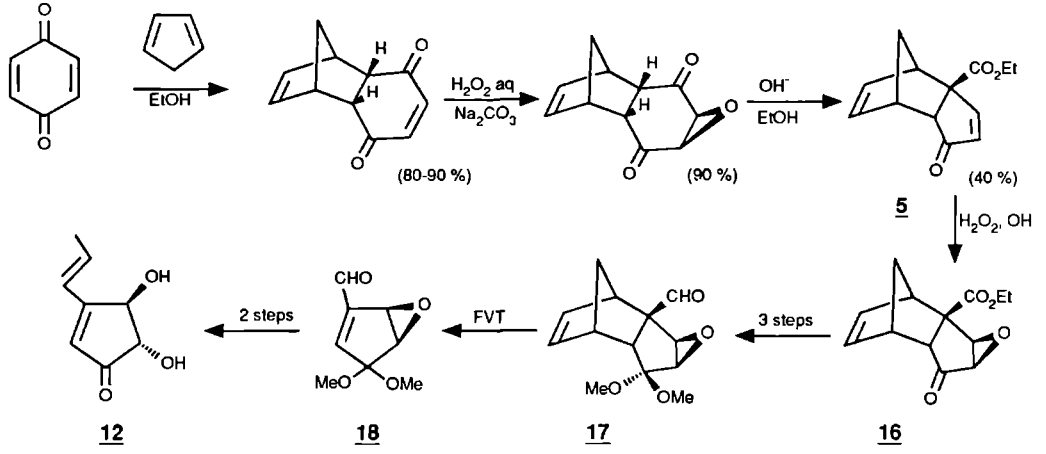
skeleton of **1** with the *endo*-configuration, the stereochemical course of the reactions at the enone function is well defined. For instance, a conjugate nucleophilic addition in **1** will preferentially take place from the *convex* side of the molecule, stereospecifically giving the *exo*-substituted product. This strategy of Scheme 3 enables the stereocontrolled synthesis of a variety of functionalized cyclopentenones. Interesting examples are reported in the literature[14], *viz.* the cyclopentanoid natural products terrein **12**[15], dihydrojasmon **13**[16], dihydrosarkomycin **14**[16] and pentenomycin **15**[17].



12 **13** **14** **15**

The synthetic sequence leading to the mould metabolite terrein **12** is outlined in Scheme 4. The stereospecific epoxidation of **5**[18] to form **16** and the thermolysis of **17** to produce **18**, should particularly be noted.

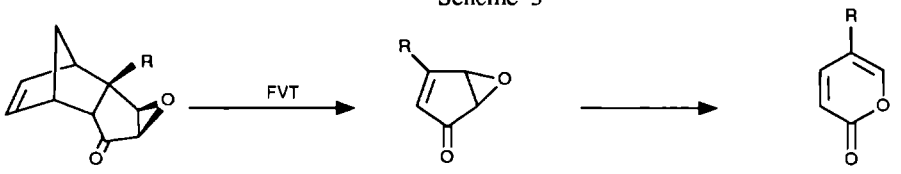
Scheme 4



A complication that may play a role during the thermolysis of epoxides **19**, derived from **1**, is a further rearrangement of the initially formed cyclopentadienone oxides **20** into the α-pyrones **21** (Scheme 5). With analogous epoxides derived from the oxa-compound **6**, the temperature required for the thermal cycloreversion is considerably lower and therefore the further rearrangement of epoxides **20** is usually avoided[11].

A special property of the tricyclodecadienones **1** is their intrinsic chirality. This implies that these tricyclic compounds can be considered as chiral synthetic equivalents of cyclopentadienone. Hence, when enantiomerically pure tricyclodecadienones **1** are used in a synthetic sequence and the chemical

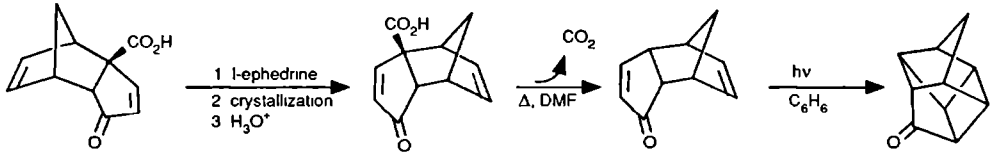
Scheme 5



19 **20** **21**

transformations of their enone moiety take place stereoselectively (*vide supra*), the ultimate product, after flash vacuum thermolysis, is also enantiomerically pure. Homochiral tricyclodecadienones that can be used in the enantioselective synthesis of cyclopentenoids were obtained from the carboxylic acid **22** or its ester **5**. Classical resolution of **22**, using l-ephedrine, gave the carboxylic acid (-)-**22** with a high optical purity (ee>93 %)[19] (Scheme 6). Decarboxylation of (-)-**22** leads to the homochiral parent

Scheme 6

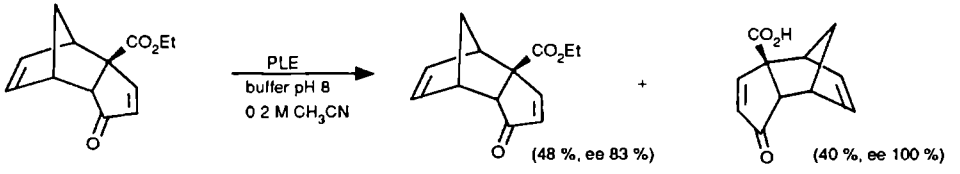


22 (-)-**22** (+)-**23** (+)-**24**

system (+)-**23**. The absolute configuration was established by correlation with the known optically pure 1,3-bishomocubanone (+)-**24**[20].

An alternative preparation of enantiomerically pure tricyclodecadienones makes use of the kinetic resolution with enzymes[21] (Scheme 7). The acid (-)-**22** was obtained enantiomerically pure. Starting

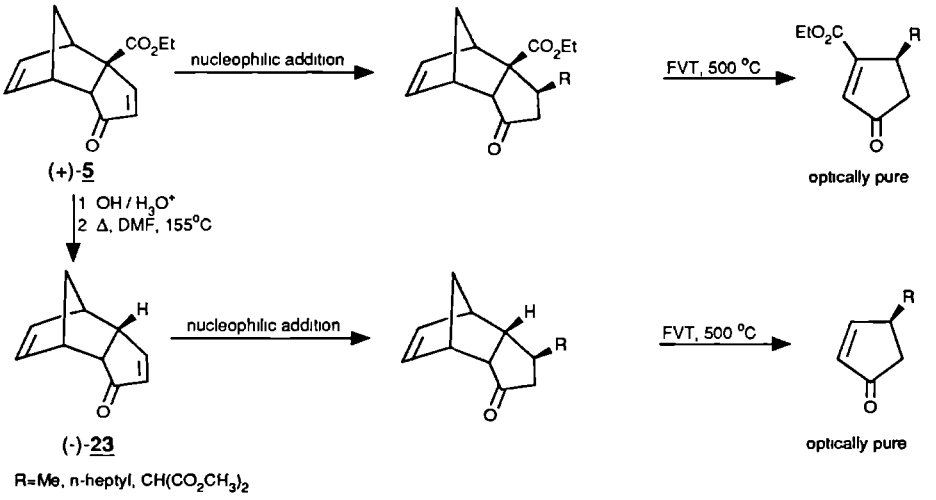
Scheme 7



(±)-**5** (+)-**5** (-)-**22**

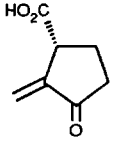
from these homochiral tricyclodecadienones **5**, (**22**) and **23**, some optically pure cyclopentenones were obtained[21] as is illustrated in Scheme 8.

Scheme 8



1.2 OBJECTIVES OF THIS STUDY

The attractive features of the tricyclodecadienones **5**, **22** and **23** are their easy availability from relatively cheap materials, their rigid *endo*-configuration, causing strict stereochemical control of conjugate addition reactions and their intrinsic chirality which, after an optical resolution, enables the synthesis of optically pure cyclopentenoids. Hitherto, tricyclodecadienones **1** were only used for the preparation of cyclopentenoids with an endo-cyclic olefinic moiety. The objective of the study presented in this thesis is to extend the scope of the synthetic strategy, based on these tricyclic systems, to the preparation of cyclopentenoids with an exo-cyclic olefinic moiety. Several naturally occurring cyclopentenoids contain an exo-cyclic enone function and therefore are appropriate targets for this study. Examples are sarkomycin **25**[22-24], an antitumor compound and the antibiotics methylenomycin A **26**, methylenomycin B **27**[25,26] and xanthocidin **28**[27,28].



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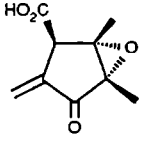

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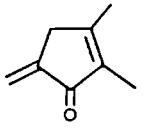

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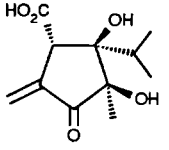

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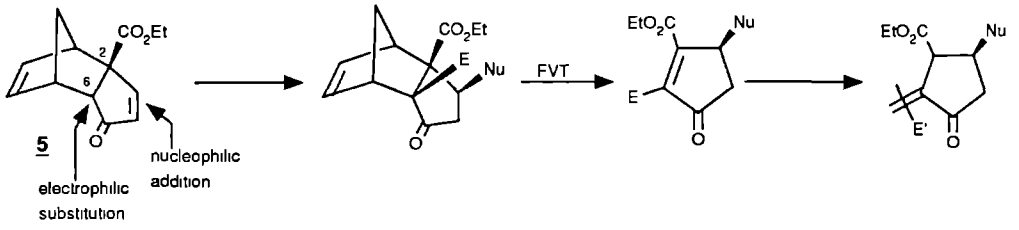
The synthetic concept for the preparation of such cyclopentenoids is depicted in Scheme 9. The tricyclic ester **5** is an attractive (chiral) synthon for this study as it already contains the desired carboxylic acid function at the correct position. In this thesis the synthetic prospects of the tricyclodecadienone system will be further evaluated with emphasis on the concepts depicted in Scheme 9. Sarko-

mycin 25 and some of its analogues serve as target molecules.

Scheme 9

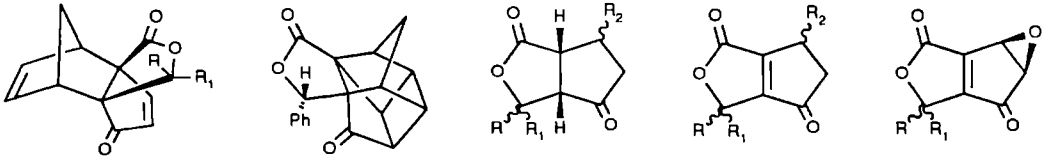


1.3 OUTLINE OF THIS THESIS

In **Chapter 1** the synthesis and chemical properties of tricyclo[5.2.1.$0^{2,6}$]decadienones are briefly reviewed, in connection with their use as synthons for functionalized cyclopentenones. Also the objectives of this study and an outline of the thesis are included.

Angular alkylation reactions[29] of tricyclic ester 5 with several primary alkyl halides are described in **Chapter 2**. Furthermore, the implications of angular alkylation for the skeletal integrity of 5 were studied[30]. Starting from ester 5, a new synthetic route to dihydrosarkomycin 14 and some of its analogues was accomplished. Details of the FVT apparatus and the experimental procedure are described in the appendix of this Chapter.

In **Chapter 3** the angular condensation of tricyclic ester 5 with various aldehydes and ketones is reported. In addition, the chemical behavior of the thus obtained tetracyclic lactones 29 toward conjugate addition reactions is described[31], with emphasis on the stereochemistry of these reactions. Finally, the potential of lactone 29 for the synthesis of the annelated cage compound 30 is demonstrated.

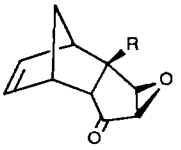


29 30 31 32 33

Chapter 4 deals with the synthetic route to sarkomycins, using lactones 29 as starting materials. It is shown that the sarkomycin precursors 31 can be obtained in three steps. Special attention has been given to the stereoselectivity during the reduction of substituted cyclopentenoid butenolides 32. It is demonstrated that in some cases the applied reduction directly gave sarkomycin analogues. In addition, a two-step conversion of the [4.3.3]oxapropellanes 29 into the annelated cyclopentadienone oxides 33 is described.

Chapter 5 deals with the conversion of optically pure ester 5 into optically pure cyclopentenoids

32. It is shown that this reaction sequence proceeds with complete retention of stereochemical integrity.



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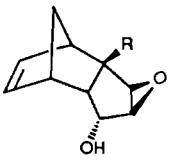

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In **Chapter 6** the reduction of epoxytricyclodecenones 34 is described. Reaction of 34 with LDA surprisingly gives the reduction product 35. The thermal behavior during the flash vacuum thermolysis of 35 is described and compared with the results reported in the literature[32].

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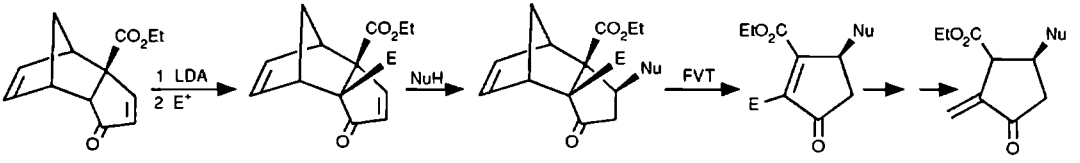
CHAPTER 2

ANGULAR ALKYLATION OF 2-CARBOETHOXYTRICYCLO[5.2.1.$0^{2,6}$]DECADIENONE AND ITS IMPLICATIONS FOR THE SKELETAL INTEGRITY OF THE TRICYCLODECADIENONE SYSTEM

2.1 INTRODUCTION

In the preceding Chapter it was demonstrated that tricyclo[5.2.1.$0^{2,6}$]decadienones are useful synthons for a variety of functionalized cyclopentenones, containing an endo-cyclic double bond, with defined stereochemistry and chirality[1,2]. The aim of the study presented in this Chapter is to extend the scope of the synthetic strategy based on these tricyclic systems to the preparation of cyclopentenones with an exo-cyclic olefinic moiety. Several naturally occurring cyclopentenoids contain an exo-cyclic enone function and therefore are appropriate targets for this study. Examples are sarkomycin, an antitumor compound, and the antibiotic methylenomycin B (see Chapter 1). The proposed sequence of events is depicted in Scheme 1. Angular functionalization of the readily available[3] tricyclic ester **1**, followed by a conjugate nucleophilic addition to the enone function, is expected to produce compound **3**. Subsequent application of the technique of Flash Vacuum Thermolysis (FVT) will furnish cyclopentenone **4**, which then in a series of transformations hopefully can be converted into the desired exo-cyclic product **5**.

Scheme 1



1 **2** **3** **4** **5**

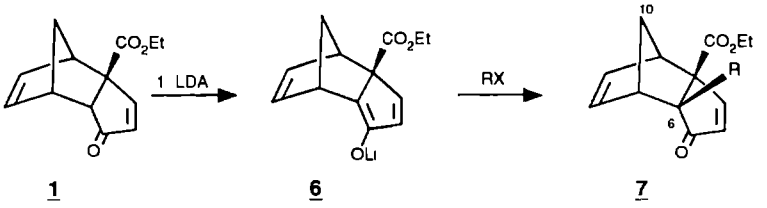
This Chapter deals with the apparently simple angular alkylation, *viz.* the conversion of **1** into **2** with the electrophile being an alkylating agent[4]. Furthermore, the chemical properties of the thus-prepared angularly alkylated tricyclic compounds, in particular their skeletal integrity will be discussed in detail[5].

2.2 ANGULAR ALKYLATION OF ETHYL TRICYCLODECADIENONE 2-CARBOXYLATE **1**

For the angular deprotonation of tricyclic ester **1**[3] a nonnucleophilic and strong base is most appropriate in order to avoid undesired reactions of both the enone- and carboethoxy group. With LDA in dry THF at -78 °C, a clean deprotonation at the 6-position of ester **1** was accomplished furnishing lithium enolate **6** (Scheme 2). The intermediacy of this anion was established by quenching with an excess of D_2O, which gave the corresponding 6-deuterated enone **1** in high yield. Alkylation of **1** was

carried out by adding alkyl halides at -78 °C and slowly raising the temperature to 20 °C .

Scheme 2

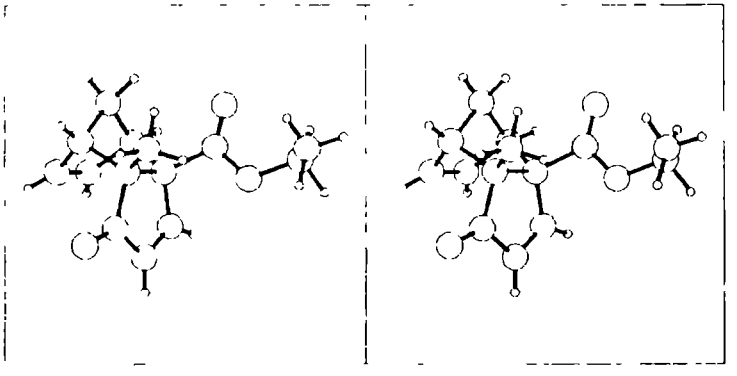


1 6 7

7	R	X	yield (%)
a	methyl	I	88
b	ethyl	I	77
c	allyl	I	68
d	n-heptyl	I	47
e	benzyl	Br	28
f	CH_2I	I	8

Electrophilic substitution of **6** with methyl iodide led stereospecifically to the corresponding 6-methylated enone ester **7a** in 88 % yield. Addition of other primary alkyl halides, such as ethyl iodide, allyl bromide and *n*-heptyl iodide, similarly gave **7b-d**. However, with benzyl bromide as the electrophile, a mixture of products was obtained, containing 6-benzyl ester **7e** in a yield of 28 %, together with 1,2-diphenyl-1-bromoethane and unreacted **1**. The recovery of starting material **1** can readily be explained by assuming competitive proton exchange of enolate **6** with benzyl bromide, giving a benzyl carbanion that on coupling with another benzyl bromide produces 1,2-diphenyl-1-bromoethane. Most likely, the introduction of a relatively bulky benzyl group eclipsed with the ester function at C_2 will cause considerable steric interaction and consequently will retard the formation of the 6-substitution product **7e**. To a certain extent, this steric interaction exists in all angularly substituted enones **7** and is directly dependent on the steric bulk exerted by the group introduced, as will be demonstrated later. Reaction of **1** with diiodomethane yielded a mixture of products consisting

Fig. 1



of iodide **7f**, starting ester **1** and polymeric material. After flash chromatography pure **7f** was obtained in a yield of 8 % only, implying that further annelation reactions[6] of **1**, based on angular iodomethylations are not promising. The structures **7a-f** were ascertained by their spectral data. Interestingly, their NMR-spectra differ markedly from **1**, *e.g.* the *syn*-bridge proton at C_{10} is considerably

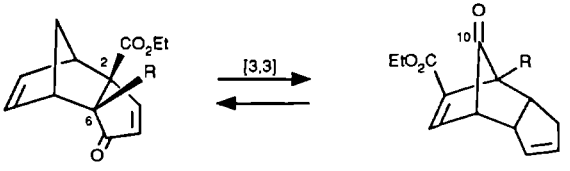
shifted to lower field (~0.4 ppm). This difference may be explained by assuming a Van der Waals interaction[7] of this proton with the angular alkyl group. Structure **7a** was unequivocally established by an X-ray diffraction analysis[8] (Fig. 1).

2.3 REACTIONS OF ANGULARLY 6-ALKYLATED ETHYL TRICYCLODECADIENONE 2-CARBOXYLATES 7

2.3.1 THE COPE REARRANGEMENT

During the synthesis of the angularly alkylated tricyclodecadienones **7** a considerable diminished chemical stability of the tricyclic enone system was encountered. Alkylation of **1** with methyl iodide smoothly afforded **7a** in a high yield as a single crystalline compound. Surprisingly, upon standing at room temperature for some days, these crystals slowly deliquisced. ^{1}H-NMR spectroscopy revealed the formation of a mixture containing **7a** and its isomer **8a**. The formation of **8a** results from a sigmatropic [3,3] rearrangement (Cope rearrangement), as is depicted in Scheme 3. The observation of a high C=O absorption (1780 cm^{-1}) in the IR-spectrum of **8a** clearly indicates the presence of a strained carbonyl function.

Scheme 3



7 **8**

	R	**7**(%)	**8**(%)
	H	100	-
a	methyl	65	35
b	ethyl	35	65
c	allyl	40	60
d	n-heptyl	35	65
e	benzyl	25	75
f	CH_2I	40	60

After standing for approximately a week an equilibrium between **7a** and **8a** was reached with a molar ratio amounting to 65:35. Analogously, all other 6-alkyl enone esters **7** show this sigmatropic equilibration, however at a much higher rate and in favor of the rearranged product **8**. In contrast, ester **1** exhibits no Cope rearrangement, neither at room temperature nor at elevated temperatures. The position of the equilibria in these rearrangements could be easily determined from the corresponding ^{1}H-NMR spectra in which several signals are well separated.

Apparently, angular substitution at C_6 in enone ester **1** leads to such highly congested structures **7** that [3,3] sigmatropic rearrangement to **8** becomes thermodynamically favorable. It appeared that the equilibrium between **7** and **8** in these experiments is shifted in favor of **8** when the steric bulk of the 6-substituent is increasing. The rationale for this is the greater steric interaction between the group R and the 2-carboethoxy group in **7**, and as a consequence, raising their ground state energies. Force Field calculations using Allinger's MM2-program, seem to confirm this hypothesis, although these values must be interpreted with extreme care. An increase in steric volume of the group R at C_6 in **7**

enhances the total steric energy due to an increase of the Van der Waals repulsion between the group R and the adjacent ester function (see Table 1) In the rearranged structures **8a-f** such an interaction between the ester function and the 7-alkyl group affects the respective ground state energies to a less extent It should be noted that when R=*n* heptyl or benzyl, the calculated MM_2-energies do not correspond with the position of the equilibria between **7** and **8**, as determined by ^{1}H-NMR spectroscopic measurements (Scheme 3)

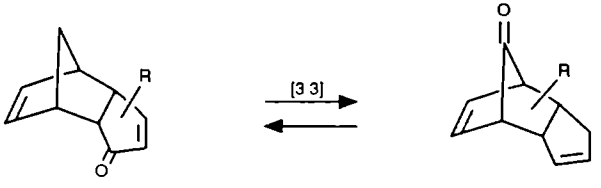
An effect of possible geometrical changes on this Cope rearrangement, situating the involved olefinic functions in a more favorable position, seems to be of minor importance[9] because the results of both MM2-calculations[10] and X-ray diffraction studies[8,11] of the parent ester **1** (Fig 1) and methylated ester **7** demonstrate that the orientation of the C_3-C_4 and C_8-C_9 bond hardly changes with the increasing steric volume of the 6-substituent

Table 1 MM_2 energies in kcal/mol

	R	7	8
	H	39 6	45 3
a	Me	42 5	45 3
b	Et	46 7	47 1
c	allyl	44 2	46 6
d	n heptyl	49 2	51 2
e	benzyl	48 2	51 4

Although Cope rearrangements are familiar processes in *endo* tricyclodecadienones[12], these [3,3] sigmatropic rearrangements seldom occur at ambient temperatures because the rearranged product **10** contains a rather strained bridged ketone function and there is loss of conjugative stabilization by disruption of the α,β-enone system in **9** (Scheme 4) As a result the ground state energy of the rearranged product **10** is generally much higher than that of **9**

Scheme 4

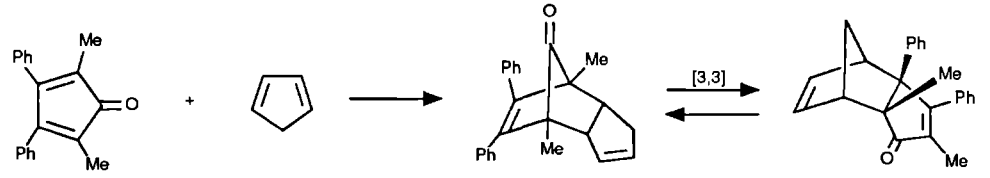


9 **10**

Hitherto, only two cases have been reported[13] in which a tricyclodecadienone and its rearranged bridged ketone are of comparable energy and, as a consequence, equilibrate in a Cope rearrangement

(Scheme 5). In all other cases, the enone is thermodynamically much more stable and no Cope rearrangement is observed. Reaction of 2,5-dimethyl-3,4-diphenylcyclopentadienone **11** with cyclopentadiene afforded *endo*-ketone **12**. When **12** was heated at 105 °C, a rapid equilibrium with **13** was established, consisting of about 50 % of both **12** and **13**.

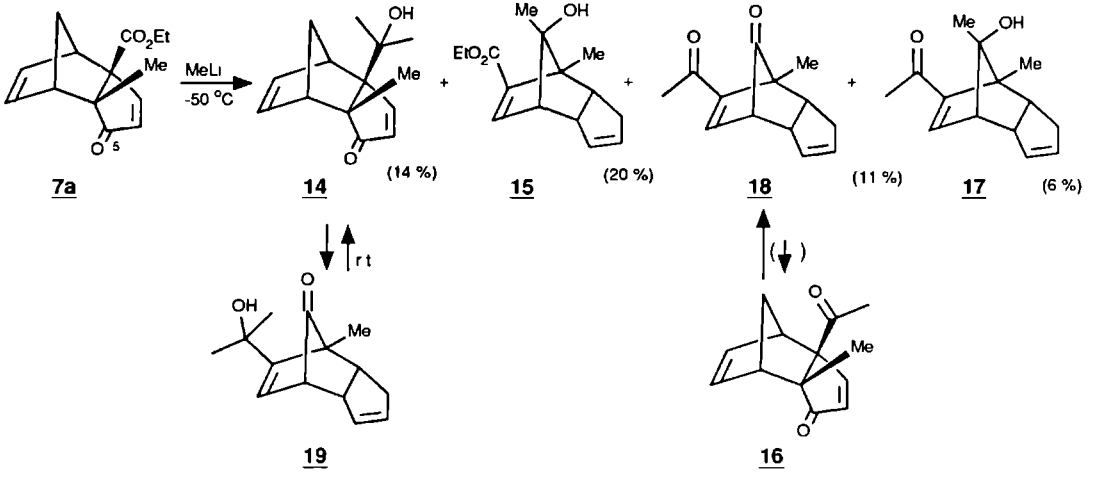
Scheme 5



11 **12** **13**

Apparently, the energetic effect of the strained carbonyl function in **12** and that of the steric hindrance of the 2-methyl and 6-phenyl group together with conjugative stabilization in **13** are in balance. A similar explanation can be given for the equilibration between **7** and **8**. In **7** there is the steric effect of the 6-alkyl group and the 2-ester function, while **8** has a highly strained bridge carbonyl function. The loss of conjugative stabilization for the enone moiety in **7** however is largely compensated by the α,β-unsaturated ester group in **8**.

Scheme 6



7a **14** **15** **18** **17**

19 **16**

In order to establish the effect of the conjugative stabilization of the substituent at C_2 on the Cope equilibration of 6-alkyl substituted tricyclodecadienones, the synthesis of 6-acetyl derivative **16** was undertaken. Attempts to prepare **16** were carried out by treating **7a** with MeLi in THF at -50 °C. Several products were obtained among which carbinol **14** (14 %), bridge methyl alcohol **15** (20 %),

the Cope product of **16**, *viz* **18** (11 %) and ketone alcohol **17** (6 %) (Scheme 6) These products can readily be explained by invoking the addition of MeLi to the various electrophilic centers of **7a**

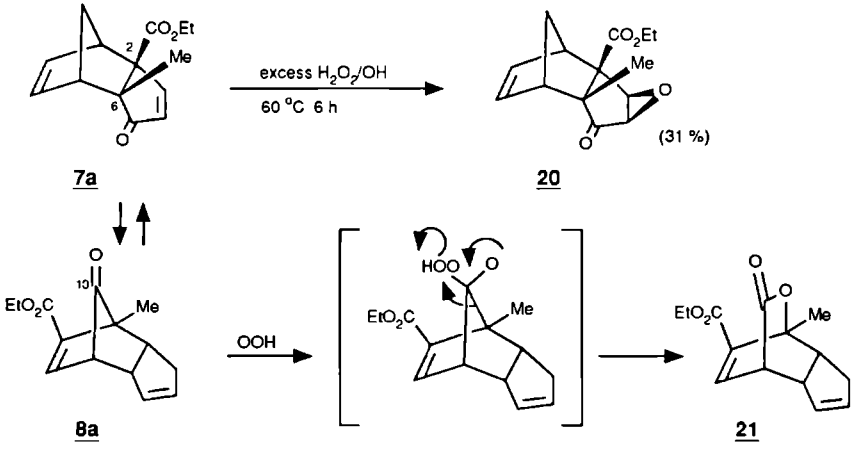
Carbinol **14** is resulting from a double addition of methyllithium at the ester function of **7a** It is of interest to note that **14**, on standing at room temperature, slowly rearranges to its Cope isomer **19** (equilibrium ratio 1 1) Bridge alcohol **15** is formed by stereoselective addition of MeLi to the C_5-keto function in **7a**, followed by a Cope rearrangement It should be noted that at the temperature of the reaction no Cope rearrangement of the starting material **7a** has been observed (*vide supra)* Product **18** is clearly the result of an initial formation of **16**, followed by a Cope rearrangement The non-rearranged product **16** was not detected Attempts to equilibrate compound **18** with **16**, *e g* by heating in CCl_4 at reflux, were not successful This result suggests that **18** has a greater thermodynamic stability than the corresponding ester **8a**

Finally, ketone alcohol **17** is formed by attack of methyllithium to both the ester and 5-keto group in **7a**, followed by a Cope rearrangement

2 3 2 NUCLEOPHILIC ADDITION TO 6 METHYLTRICYCLODECADIENONE 2-CARBOXYLATE

In the preceding Section it was shown that the introduction of an angular substituent at C_6 in ester **1** has a considerable effect on its skeletal stability, thereby facilitating the occurrence of a Cope rearrangement The presence of a 6-alkyl group in enones **7** also has a notable influence on their aptitude to undergo conjugate nucleophilic addition Alkaline epoxidation of **1** with H_2O_2 proceeds smoothly at room temperature to afford the corresponding epoxide in high yield[1], methyl enone **7a**, however, could not be epoxidized at all under these conditions It should be noted that in all experiments with **7**

Scheme 7

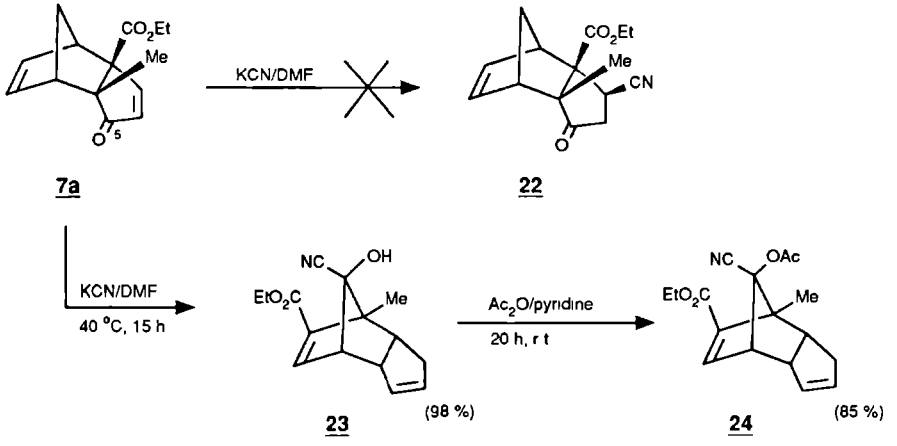


at temperatures over 50 °C, the actual starting material consists of an equilibrium mixture of **7** and **8** Only after prolonged heating at 60 °C, epoxide **20** was obtained in a modest yield of 30 % and in a

poorly reproducible reaction. In this epoxidation reaction lactone **21** was isolated as a by-product in 10 % yield. Its formation probably takes place by nucleophilic attack of the hydrogenperoxide anion (OOH^-) at the strained C_{10}-carbonyl group of **8a**, followed by Baeyer-Villiger type oxygen insertion, selectively leading to lactone **21** (Scheme 7). This lactone **21** was independently prepared from **8a** in high yield by treatment with hydrogenperoxide in acetic acid[14].

The reluctance of the enone moiety in **7a** to undergo nucleophilic additions is also demonstrated by the results of hydrocyanation experiments. Using reaction conditions similar to those applied by Rouessac *et al*[1] for the successful hydrocyanation of the parent tricyclodecadienone, no β-keto nitrile **22** was obtained at all. Instead, a cyanohydrol was isolated in excellent yield, to which tentatively structure **23** was assigned (Scheme 8). In order to establish the mechanistic pathway underlying its stereoselective formation, the configuration at C_{10} in **23** was needed. Therefore, the corresponding acetate was prepared by reacting **23** with Ac_2O in pyridine. This crystalline compound was subjected to an X-ray analysis[15] (Fig. 2) revealing structure **24**.

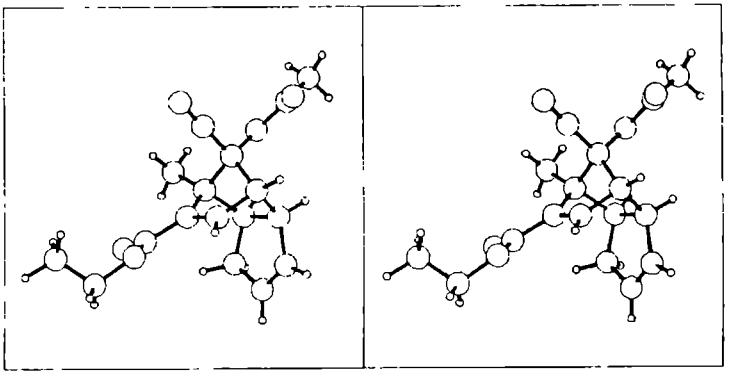
Scheme 8



The formation of **23** from **7a** can be rationalized in two ways: *i.* initial stereoselective 1,2-addition of cyanide ion to the 5-carbonyl function in **7a**, followed by a fast [3,3] sigmatropic rearrangement (Cope rearrangement) or *ii.* initial [3,3] sigmatropic rearrangement of **7a** into **8a** followed by a stereoselective cyanide addition to the strained C_{10}-keto function (Scheme 9). On the basis of independent experiments with both **7a** and **8a** the formation of **23** is most satisfactorily explained by route *ii.* The addition of cyanide to the strained C_{10}-keto group of **8a** to give **23** was complete within 1 hour at room temperature, whereas the reaction of **7a** with cyanide after 60 hours at room temperature resulted only in a mixture containing both **7a** and **23**, but no Cope rearranged compound **8a**.

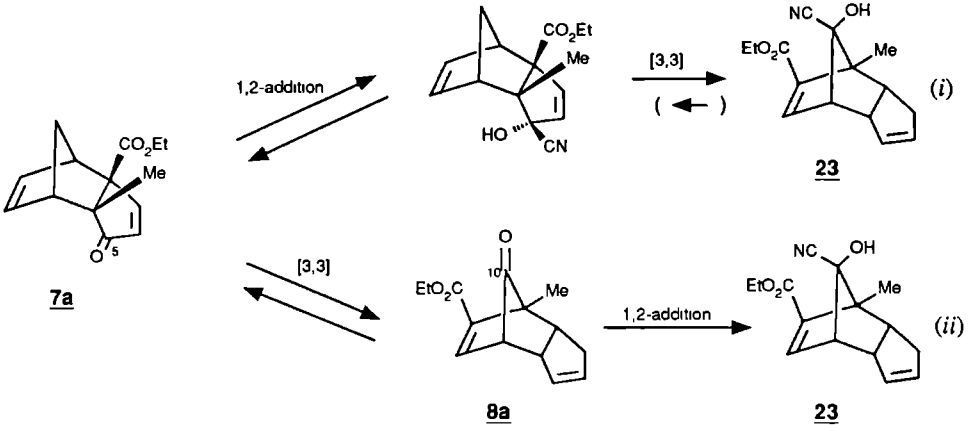
These results strongly suggest that **7a** itself either does not react with cyanide at all or only very slowly, while **8a**, as soon as it is formed from **7a**, is immediately converted into **23** in a stereoselective

Fig. 2



manner, thereby shifting the Cope equilibrium between **7a** and **8a** toward the latter compound. By carrying out this hydrocyanation at 40 °C, **7a** was quantitatively converted into cyanide **23** within 15 hours.

Scheme 9

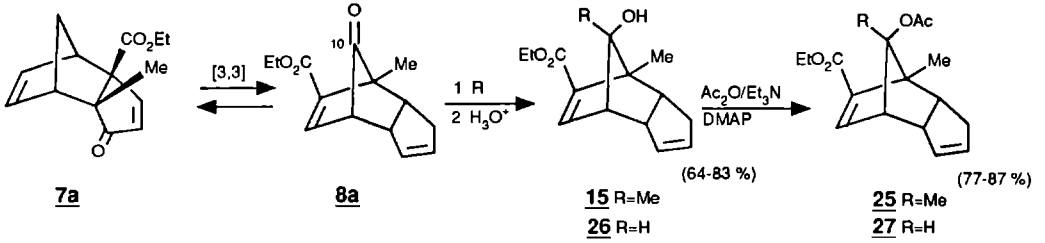


The observed stereoselective formation of **23** from **7a** is probably of steric origin (kinetic control). As will be pointed out below, the stereochemical course of this reaction is the same as in the kinetically controlled addition of MeLi or MeMgI/Cu(I)Cl to **8a** (Scheme 10).

The diminished nucleophilic reactivity of the enone function of **7a** is also encountered when a 1,4-addition with methylmagnesium iodide in the presence of Cu(I)Cl[1] was attempted. Instead of undergoing conjugate addition with the Grignard reagent, preference is given to a reaction with the C_{10}-carbonyl group of **8a** at ambient temperature (**8a** is slowly formed from **7a**), to produce stereoselectively bridge alcohol **15**. An X-ray diffraction analysis[16] of the corresponding acetate **25** (Fig. 3)

revealed the configuration at C_{10}, indicating that addition of MeMgI/Cu(I) occurred in the same stereochemical fashion as was observed for the cyanide addition to **8a**. The formation of **15** can again be explained by either an initial 1,2-addition of the organometallic to **7a**, followed by a Cope rearrangement[17] or by a direct addition to the C_{10}-carbonyl function of the rearranged product **8a**. In view of the results obtained with the cyanide addition and the high reactivity of **8a** toward methyllithium (*vide infra*), the latter explanation seems more likely.

Scheme 10

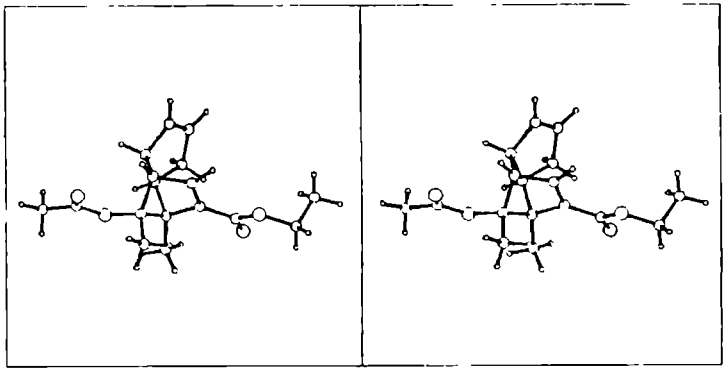


7a **8a** **15** R=Me, **26** R=H **25** R=Me, **27** R=H

Addition of methyllithium to **8a** at -78 °C leads to bridge alcohol **15**. The reduction of **8a** with $NaBH_4$ in methanol at room temperature rapidly gave alcohol **26** as the sole product. Subsequent acylation produced compound **27**. These results strongly suggest that the observed stereoselectivity for these nucleophilic additions to the C_{10}-keto function of **8a** is general for this class of compounds.

Recently, the stereoselective preparation of the corresponding methyl ester of **26** has been described[17] by treatment of the methyl ester analogue of **7a** with $NaBH_4$ in methanolic $CeCl_3.6H_2O$.

Fig. 3



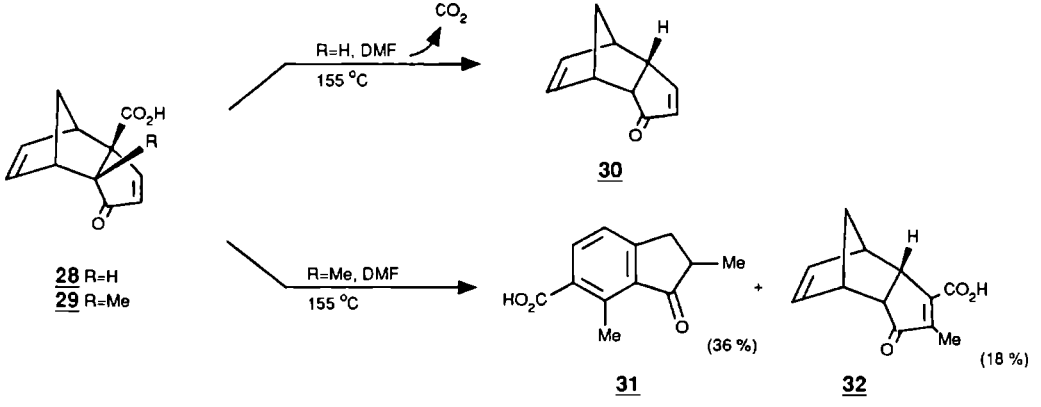
The results described above allow the conclusion that the conformationally rigid, angularly substituted ester **7a** displays a very low tendency to undergo conjugate enone addition, but preferably escapes *via* Cope equilibration into **8a**, whose C_{10} strained carbonyl group readily and stereoselectively

reacts in a kinetically controlled addition. The reluctance of **7a** to undergo 1,4-addition is probably due to severe steric interaction between the incoming nucleophile, the 2-ester group and the 6-alkyl substituent, because if this nucleophilic addition process would take place, all three groups would be positioned on the same *convex* face of the tricyclodecadienone system. The stereochemical outcome of the cyanide addition to **8a** is in agreement with the results reported by Gassman and Talley[18], who described the hydrocyanation of bicyclo[2.2.1]hept-2-en-7-one. These authors found that treatment of the last-mentioned compound with KCN in acetic acid led to a highly stereoselective *syn*-addition to its strained carbonyl group. However, no explanation for the stereoselectivity was given. The preference for *syn*-attack at the C_{10}-position of **8a** can be understood by assuming that there is considerable shielding of the carbonyl function in **8a** for *anti*-attack by both eclipsed C_2 and C_6 hydrogen atoms. Probably, the observed stereoselectivity[19] does not arise from participation of the unsaturated ester moiety of **8a** in some complexation with the nucleophilic reagent (anchimeric effect).

2.3.3 THERMAL GENERATION AND REACTIONS OF 2-ALKYL-3-CARBOETHOXYCYCLOPENTADIENONES

As reported in Section 2.3.1 6-alkyl substituted tricyclodecadienones **7** are thermodynamically considerably less stable than the parent ester **1** and rapidly undergo a skeletal Cope rearrangement. As will be shown below, the alkyl substituted esters **7/8** exhibit an unexpected and facile cycloreversion to give 2-alkyl cyclopentadienone 3-carboxylates upon heating in solution[4]. It should be noted that in all thermal experiments carried out with **7**, the actual starting material consists of an equilibrium mixture of **7** and **8**.

Scheme 11

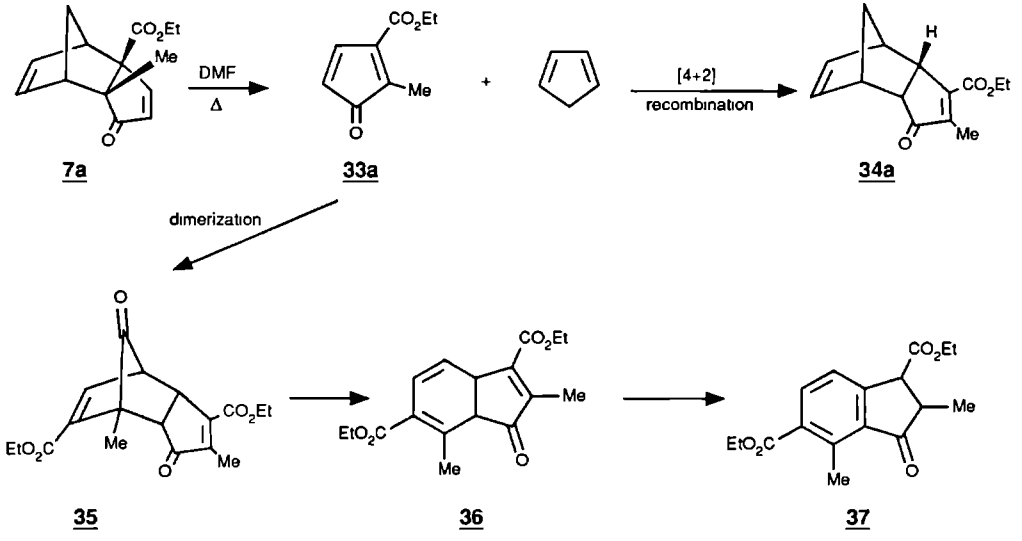


An interesting difference in thermal behavior was encountered when the parent acid **28** and the angularly methylated acid **29** were subjected to decarboxylation. Acid **28**, being a vinylogous β-keto carboxylic acid, upon heating in DMF at 155 °C, readily decarboxylates to furnish the parent tricyclo-

decadienone **30** (R=H) in 83 % yield[2,3]. Interestingly, under these conditions, **29** did not show such a decarboxylation, but instead produced a mixture of indanone **31** and the novel tricyclodecadienone **32** as the major products, in yields of 36 % and 18 %, respectively (Scheme 11).

Under similar thermal conditions, 6-methyl substituted ester **7a** was rapidly converted into a mixture of indanone ester **37** and tricyclic β-enone ester **34a**, in yields of 38 % and 19 %, respectively (Scheme 12). This concurrent formation of **37** and **34a** during the thermolysis of **7a** in DMF can readily be rationalized by assuming a [4+2] cycloreversion as the initial step to form cyclopentadienone **33a** and cyclopentadiene. Subsequently, **33a** partly recombines with cyclopentadiene to afford tricyclodecadienone **34a**, having a reversed regiochemistry in comparison with the starting material. The stability of **33a** is apparently sufficiently large to find another cyclopentadienone molecule to dimerize with. This dimerization results in the regioselective formation of tricyclic diketone **35**. Under the thermal conditions applied, subsequent decarbonylation occurs to form dihydroindenone **36**, that aromatizes to indanone **37**. In the case of the carboxylic acid analogue, subsequent decarboxylation leads to **31** (Scheme 11).

Scheme 12



7a **33a** **34a**

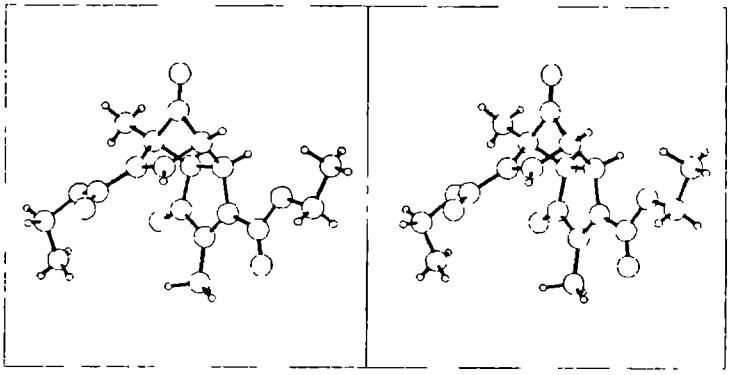
35 **36** **37**

The intermediacy of free cyclopentadienone **33a** was proven by carrying out a crossed Diels-Alder reaction with cyclopentadiene. The addition of a twentifold excess of this diene to a solution of **7a** in DMF and heating this mixture at 155 °C for 2.5 hours, afforded ethyl 4-methyl-tricyclodecadienone 3-carboxylate **34a** in the high yield of 79 %.

The occurrence of dimer **35** as precursor for indanone **37** could be proven independently by subjecting **7a** to gas phase thermolysis (450 °C, 4.10^{-2} torr). Details on this gas phase thermolysis will be

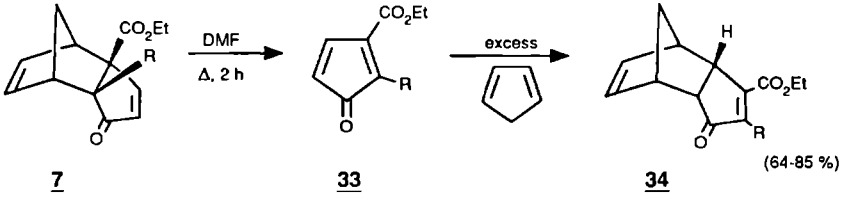
discussed in Section 2.3.5. Dimer **35** turned out to be the major product in this thermolysis. Its structure could unequivocally be established by an X-ray diffraction analysis[20] (Fig. 4). Subsequent heating of **35** in DMF caused rapid decarbonylation to give indanone **37** as the sole product.

Fig. 4



The thermal behavior of **7a** in DMF appeared to be typical for 6-alkyl substituted tricyclodecadienone-2-carboxylates. In all four other cases studied, the thermolysis proceeded smoothly to generate the corresponding 2-alkyl-cyclopentadienone esters **33b-e**, which again were trapped with added excess of cyclopentadiene, to afford tricyclic enones **34b-e** in good yields (Scheme 13). This efficient generation of **33** and its smooth regiospecific cycloaddition reaction with cyclopentadiene makes this thermolysis of practical utility. It will be shown (Section 2.4) that enone esters **34** can serve as synthons for dihydrosarkomycins.

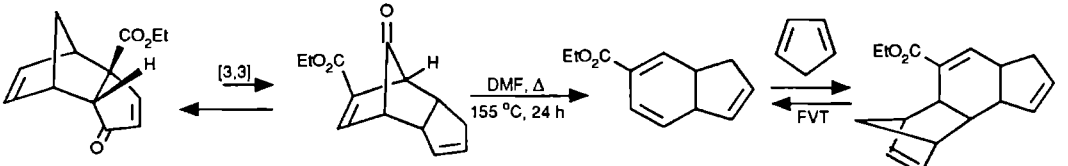
Scheme 13



In contrast to the angularly alkylated tricyclodecadienonecarboxylates **7**, parent ester **1** appeared to be thermally relatively stable when heated in DMF. Complete conversion of **1** was only achieved after 24 hours, yielding an intractable mixture. However, when the thermolysis of **1** was carried out in the presence of an excess of cyclopentadiene, with the aim to trap possible cyclopentadienone intermediates, the formation of tetracyclic ester **39** was observed in a yield of 35%, after two successive flash chromatographic purification steps. The rationale for the formation of **39** is outlined in Scheme

14. It involves the cheletropic decarbonylation of the Cope isomer of **1** and Diels-Alder reaction of the intermediate dihydroindene 6-carboxylate **38** with cyclopentadiene. There has been some controversy[21,22] about which olefinic bond of dihydroindenes react in a [2+4] cycloaddition with cyclopentadiene. In the cycloaddition of **38** with cyclopentadiene the regiochemistry is similar to that observed by Baxter and Garrath[21] for the Diels-Alder reaction of dihydroindene with cyclopentadiene. The intermediate dihydroindene carboxylate **38** could be generated by subjecting **39** to a thermal cycloreversion reaction at 525 °C by employing the flash vacuum thermolysis technique (*Cf.* Section 2.3.5).

Scheme 14



1 **8** R=H **38** **39**

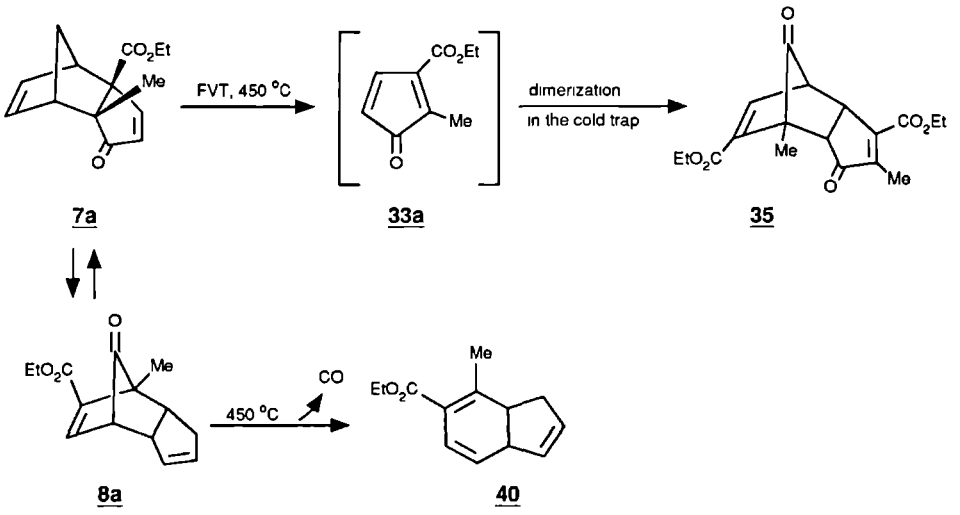
The results described in this Section allow the following conclusions. The introduction of an alkyl group at the 6-position in tricyclic ester **1** drastically alters its thermal behavior in DMF. Whereas in ester **1** thermal fragmentation proceeds by an initial Cope rearrangement, followed by a decarbonylation, 6-alkyl esters **7** fragment exclusively by a [4+2] cycloreversion. The ease at which the alkyl cyclopentadienone carboxylates **33** are formed in the last-mentioned reaction suggests a considerable stabilization of these cyclic dienones because of the presence of the electron donating 2-alkyl group as well as the electron withdrawing 3-carboxylate function (push-pull effect[23,24]). The ethoxycarbonyl substituent probably stabilizes by extending the conjugation of the enone moiety in **33**. This enhanced stability is apparently sufficient to favor the cycloreversion reaction over the alternative decarbonylation process[25]. It should be noted that, whereas the decarbonylation of tricyclodecadienones with a bridged ketone function is a well-known process[9,26], the thermal cycloreversion of such simply substituted tricyclodecadienones as **7** in solution, to generate cyclopentadienones, has no precedent[24].

2.3.4 GENERATION OF CYCLOPENTADIENONE 3-CARBOXYLATES BY FLASH VACUUM THERMOLYSIS OF TRICYCLODECADIENONE 2-CARBOXYLATES

In order to verify the intermediacy of cyclopentadienone dimer **35** during the formation of **37** in the thermolysis of **7a** in DMF (Scheme 12), the isolation of **35** was attempted by performing the thermolysis of **7a** under FVT-conditions. Under these gas phase conditions, it is expected that the cycloreversion of **7a**/**8a** will initially produce cyclopentadienone **33a** that subsequently will dimerize in the cold trap. Decarbonylation of the thus-obtained dimer **35** is now unlikely. The gas phase thermolysis yielded a mixture of the expected **35** and dihydroindene **40** in a molar ratio of 2.4:1. The formation of

40 can be rationalized by invoking a thermal cheletropic elimination of CO[26] from **8a** (Scheme 15).

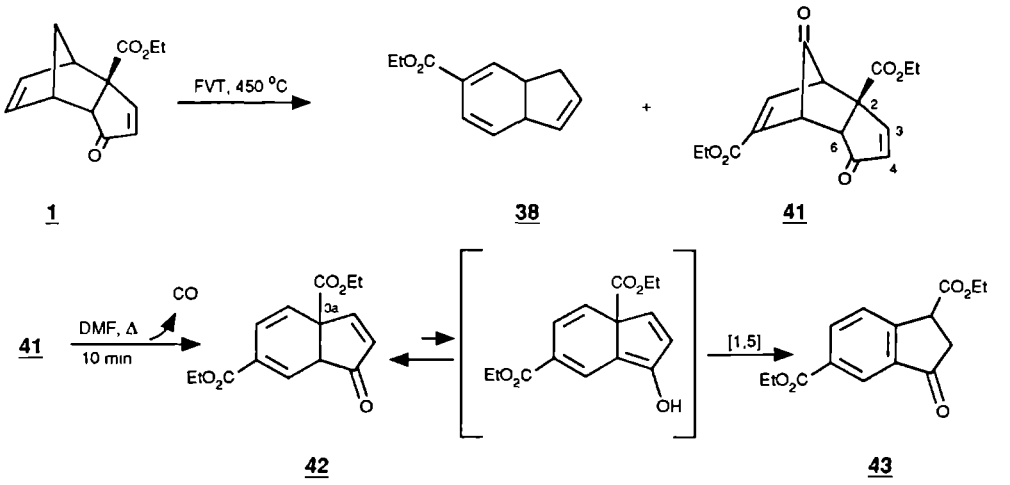
Scheme 15



By employing identical thermal conditions for parent ester **1**, a mixture of cyclopentadienone dimer **41** and dihydroindene **38**[27] was obtained in equimolar amounts (Scheme 16). The substitution pattern in structure **41** could be deduced from its ^{1}H-NMR spectrum: β-enone proton H_3 appeared as a doublet ($^3J_{3,4}$= 5.7 Hz) at δ 7.45 ppm, implying that one of the carboethoxy groups must occupy the angular 2- or 6-position. Determination of all vicinal coupling constants by performing additional homonuclear decoupling experiments revealed structure **41**. It should be noted that the orientation of the cyclopentadienones in the respective dimerizations, *i e.* **33a** to **35** and **33** (R=H) to **41**, is different. The formation of **41** shows that for **33** (R=H), the ester conjugated enone moiety is more dienophilic than the unsubstituted enone function in this dimerization. Here, the relative HOMO/LUMO energies of the respective enone moieties seem to be most important in determining the regiochemistry of the cycloaddition reaction. In contrast, the dimerization of compound **33a** leads to the predominant formation of tricyclodecadienedione **35**. Probably steric factors now determine the regiochemistry of this reaction because dimerization involving the ester substituted enone moiety would result in a highly congested tricyclodecadienedione structure with the vicinal ester- and alkyl groups in an eclipsed orientation. The observed regiochemistry in these two dimerizations with respect to the relative orientation of both ester functions, is explained by invoking minimal dipole interaction between these functions in the transition state, forcing this polar groups as far apart as possible[28]. The above experiments show that the thermal behavior of **1** and **7a** in the gas phase is very similar. Cycloreversion as well as decarbonylation are observed for both substrates, albeit in different ratios.

It should be noted that dihydroindenes **38** and **40** are both unstable compounds that decompose on standing at room temperature.

Scheme 16



Heating of **35** in DMF rapidly afforded indanone **37** in high yield (Scheme 12). Analogously, **41** was cleanly converted into **43**. Indanone **43** is most likely formed via decarbonylation of **41** to give **42**, that undergoes successively a [1,5] shift of its 3a-carboethoxy group[30] and an aromatization[24] (Scheme 16). The intermediacy of dihydroindenones **36** (*Cf.* Scheme 12) and **42** in the respective formation of **37** and **43** was confirmed by preparing these two compounds by an independent flash vacuum thermolysis (450 °C, 2.10^{-2} torr) of **35** and **41**, respectively.

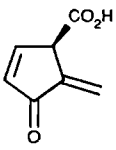
In conclusion, comparison of the thermal behavior of **1** and **7** reveals that in DMF either cycloreversion (for **7**) or decarbonylation of the Cope isomer of **1** takes place, whereas in the gas phase both processes occur simultaneously for both substrates. At the relatively low temperature of 150 °C as applied in DMF, there is much more chemoselectivity than under FVT conditions (450 °C) and as a consequence one of the electrocyclic processes predominates.

2.4 SYNTHESIS OF DIHYDROSARKOMYCINS

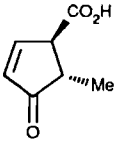
As suggested during the discussion of the Schemes 12 and 13, the efficient synthesis of tricyclodecadienones **34** from readily available ester **1** is tempting their use as synthons. In this Section their application in the preparation of some dihydrosarkomycins will be described.

Dihydrosarkomycin **45a** is completely ineffective against bacteria, however, it exhibits strong oncostatic activity[31], similar to sarkomycin **44**[32]. Some derivatives of dihydrosarkomycin, *e.g.* its homologue **45b**, were found[33] to inhibit Ehrlich ascites carcinoma even more strongly than sarkomycin **44** and dihydrosarkomycin **45a**. Some syntheses of dihydrosarkomycin have already been

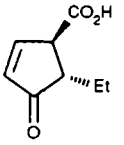
reported in the literature[34,35].



44



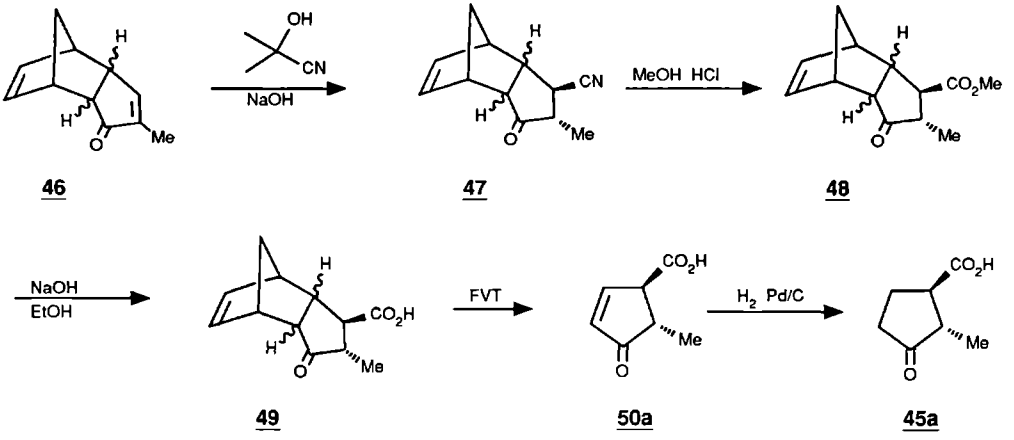
45a



45b

In our laboratory, Verlaak[35] accomplished the synthesis of dihydrosarkomycin **45a** in five steps and in an overall yield of 50 % from an *endo/exo*-mixture of 4-methyltricyclodecadienone **46** (Scheme 17)

Scheme 17



46 **47** **48** **49** **50a** **45a**

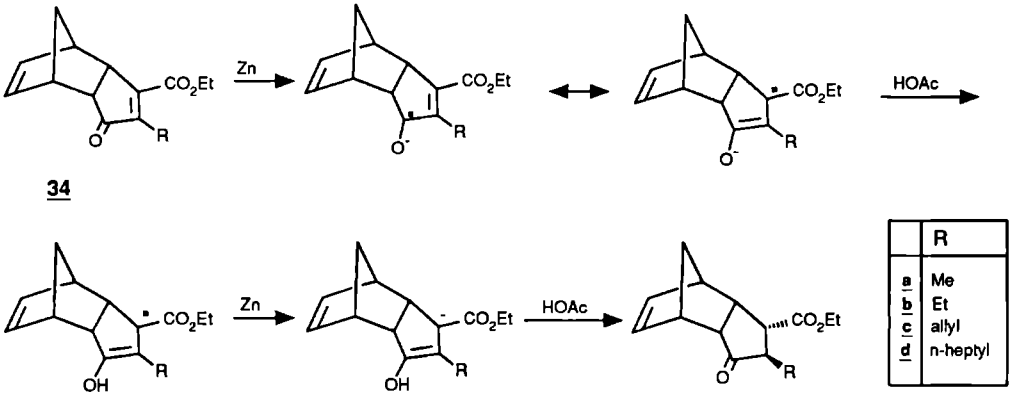
Comparing structure **48** with **34a** immediately suggests a reduction of the C_3-C_4 olefinic bond of **34a** as a possible route to **48** For this selective reduction of **34a** Ohkata's method[36] using zinc in acetic acid was chosen This method was shown to produce *trans*-products exclusively Application of Ohkata's method for the reduction of **34** indeed gave a single product with a *trans*-configuration (Scheme 18) Spectral analysis revealed however, that the reduction product has structure **51**, thus with opposite configurations at C_4 and C_5 compared with Verlaak's compound **48** The ^{1}H-NMR coupling constant $^3J_{H\ 3,4}$ in **51a** amounted to 11 7 Hz This value agrees well with that of *endo*-**48**[35] ($^3J_{H\ 3,4}$ = 12 Hz) pointing to a *trans*-relationship of the 3-carboalkoxy- and the 4-alkyl substituent in both compounds The rationale[37] for this diastereospecific formation of **51a** is depicted in Scheme 18

The observed stereospecificity in this reduction with Zn/AcOH appeared to be characteristic for all tricyclic esters **34**, because in the five cases studied, the reaction afforded *trans*-diastereomer **51** as the sole product

Apparently, the final protonation of the intermediate anion, leading to **51**, takes place exclusively

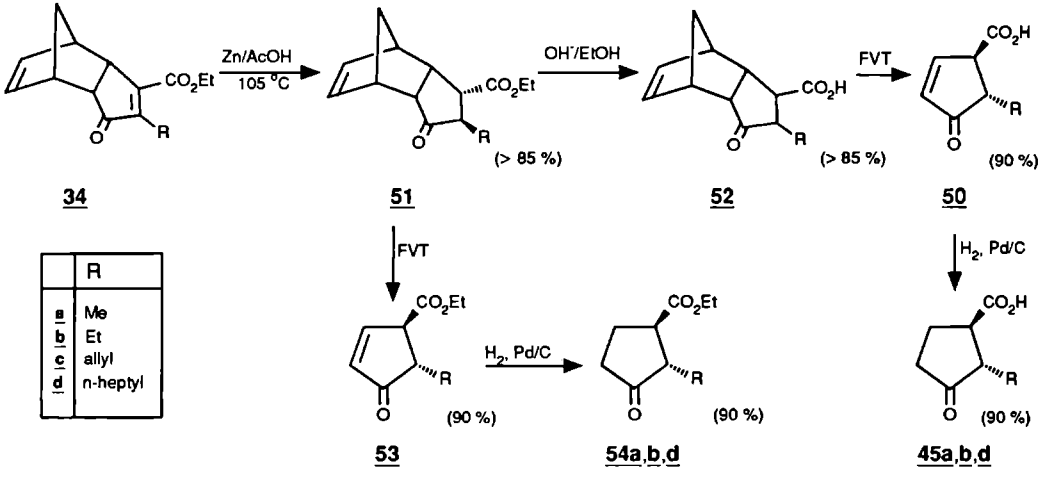
from the less hindered *convex* face of *endo*-structure **34**. By conducting this reduction in the presence of excess reducing agent (zinc) and a proton donor (AcOH) the reduction and protonation steps that follow radical anion formation are favored and accordingly diminishing competing side reactions, such as dimer formation[37].

Scheme 18



Hydrolysis of **51** in alkaline ethanol produced the corresponding carboxylic acids **52** in high yields after acid-base extraction (Scheme 19). However, these carboxylic acids **52** were obtained as equimolar *trans*-mixtures, suggesting that the alkaline reaction conditions cause an isomerization of **52** (double epimerization).

Scheme 19



Subsequent flash vacuum thermolysis (FVT) of **52** afforded the labile carboxylic acids **50** in high yields. Formally, these compounds are isomers of sarkomycins. As acids **50** were difficult to purify, they were immediately hydrogenated catalytically[35] to the desired dihydrosarkomycins **45**, which were obtained as NMR-pure compounds after acid-base extraction. The overall yields of dihydrosarkomycins **45**, calculated on **1**, amounted to 40 %. The spectral data of dihydrosarkomycin **45a** and its homologue **45b** were in good agreement with those reported in the literature[33,35]. Tricyclic esters **51** were also utilized for the synthesis of dihydrosarkomycin ethyl esters. FVT of esters **51** produced the rather stable cyclopentenone carboxylates **53a-d** in excellent yields. The cyclopentenones **53a,b,d** were subsequently converted into the desired dihydrosarkomycin carboxylates **54a,b,d** in high overall yields by catalytic hydrogenation on Pd/C, using Verlaak's conditions[35].

In conclusion, starting from tricyclic ester **1**, an efficient and general synthesis of dihydrosarkomycins **45** was accomplished. This result shows that the tricyclodecadienones **34** are indeed of synthetic importance.

2 5 EXPERIMENTAL PART

General

^{1}H-NMR spectra were recorded on a Bruker WH-90 spectrometer in $CDCl_3$ solution with $SiMe_4$ as internal reference The chemical shifts and coupling constants were obtained by first order analysis The shape of the NMR absorptions is given by the following abbreviations s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dd = doublet of doublet, br = broad ^{13}C-NMR spectra were recorded on a Bruker WP-60 spectrometer or Bruker WM200 (in $CDCl_3$) Mass spectra were obtained using a double focusing VG 7070E mass spectrometer Melting points were determined using a Reichert melting point apparatus and are uncorrected IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer UV spectra were measured on a Perkin-Elmer 555 spectrophotometer Elemental analyses were carried out in the Microanalytical Department of the University of Nijmegen Capillary GC (CapGC) analyses were performed using a HP 5790 A, containing a cross-linked methyl silicone column, L=25 m, ID=31 mm, film 0 17 µm applying a temperature program 100 °C to 250 °C, 15 °C/min (prog 2), unless indicated otherwise Flash Vacuum Thermolysis (FVT) was carried out using the FVT apparatus as developed at the Organic Laboratory of the Nijmegen University (*Cf the appendix at the end of this Chapter*) Flash chromatographic purifications (pressure (p) 1 5-2 atm) were carried out using either silica gel (Kieselgel 60 H (Merck)) or Al_2O_3 (150 neutral typ T (Merck)) TLC-spots were visualized with an UV lamp, iodine vapor or after spraying with aqueous sulfuric acid, followed by heating THF was dried by subsequent treatment with $CaCl_2$, CaH_2 and distillation from $LiAlH_4$, before use All reactions with LDA or alkyllithium compounds were performed in a nitrogen atmosphere Alkyl halides were distilled before use Glass equipment and syringes were oven-dried

Syntheses

Ethyl 5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **1**

Ester **1** was prepared *via* a modified procedure[3], originally described by Herz and co-workers, in a yield of approximately 50 % from exo-4,5 *epoxy*-endo-*tricyclo*[6 2 1 $0^{2,7}$]*undec* 9 *en*-3,6 *dione* ^{13}C-NMR δ 13 7 (OCH_2CH_3), 45 4, 49 3, 50 9, 53 8 (C_1, C_6, C_7, C_{10}), 61 4, 64 1 (C_2, OCH_2), 133 6, 134 8, 136 2 (C_4, C_8, C_9), 161 7 (C_3), 173 0 (C_2CO), 208 7 (C_5), UV (MeOH) λ_{max} 229 nm

Ethyl 6-*deuterio*-5-*oxo* endo *tricyclo*[5 2 1 $0^{2,6}$]*deca* 3,8-*diene* 2-*carboxylate* 6-*D* **1**

Monodeuterated **1** was prepared as described for **7a**, starting from diisopropylamine (0 11 g, 1 089 mmol), *n* BuLi (0 7 ml, 1 6 M soln in *n* hexane, 1 12 mmol), **1** (0 20 g, 0 917 mmol) and D_2O (0 36 g, 18 mmol) After attaining r t , Et_2O (25 ml) was added, the yellow lithium salts were removed by filtration and the filtrate was concentrated *in vacuo* Flash chromatography (silica gel, EtOAc /*n* hexane = 1/10, Rf = 0 3) afforded *6 D*-**1** (0 14 g, 70 %) as an oil ^{1}H-NMR δ 1 30 (t, J=7 0 Hz, 3H, OCH_2CH_3), 1 73 A of AB (d, J=9 0 Hz, 1H, H_{10}), 1 96 B of AB (d, J=9 0 Hz, 1H, H_{10}), 3 16-3 33 (m,

2H, H_1, H_7), 4.22 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.83-6.02 (m, 3H, H_4, H_8, H_9), 7.29 (d, J=5.8 Hz, 1H, H_3); IR (CCl_4): ν 1725 (C=O, ester), 1705 (C=O, unsat.), 1585 (C=C, unsat.) cm^{-1}; EI/MS: m/e 219 (M^+), 66 (C_5H_6); Found 219.102. $C_{13}H_{13}DO_3$ requires 219.101.

Ethyl 6-*methyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **7a**

To a stirred soln of diisopropylamine (0.17 g, 1.68 mmol) in dry THF (10 ml) was gradually added a 1.6 M soln of *n*-BuLi in *n*-hexane (1.0 ml, 1.6 mmol) at 0 °C. After 20 min the mixture was cooled to -78 °C and a soln of **1** (0.33 g, 1.514 mmol) in THF was gradually added using a syringe. After 15 min the mixture was quenched with MeI (0.30 g, 2.11 mmol) in 10 ml of THF. The yellow soln was then allowed to attain r.t. and stirred for 30 min. The resulting brown soln was treated with excess of NH_4Cl (10 % aq) at 0 °C, extracted with diethyl ether (3x50 ml), washed with water (3x20 ml), dried over $MgSO_4$ and evaporated *in vacuo*, to give crude **7a**. Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10, Rf = 0.45) afforded **7a** (0.33 g, 88 %) as an oil which slowly solidified. Recrystallization, by cooling a saturated soln of **7a** in EtOH from 20 °C to -17 °C, yielded analytically pure **7a**; m.p. 74-76 °C; ^{1}H-NMR: δ 1.26 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.30 (s, 3H, C_6-Me), 1.69-1.96 (m, 1H, H_{10}), 2.33-2.53 (m, 1H, H_{10}), 2.68-2.89 (m, 1H, H_7), 3.09-3.32 (m, 1H, H_1), 4.22 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.79-6.17 (m, 3H, H_4, H_8, H_9), 7.29 (d, J=5.8 Hz, 1H, H_3); IR (KBr): ν 3060, 2980, 1730 (C=O, ester), 1710 (C=O, enone), 1230, 1220 cm^{-1}; EI/MS: m/e 232 (M^+), 204 (M-CO), 159 (M-COOEt), 131 (M-CO-COOEt), 66 (C_5H_6); CI/MS: m/e 233 (M^++1); UV (MeOH): λ_{max} 227 nm; Found C, 72.27; H, 6.99. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94.

Ethyl 6-*ethyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **7b**

The procedure as described for **7a** was followed. Starting from diisopropylamine (0.56 g, 5.54 mmol), *n*-BuLi (4.0 ml, 6.4 mmol), **1** (1.0 g, 4.59 mmol) and EtI (1.45 g, 9.29 mmol) gave **7b** (1.291 g, crude yield). After flash chromatography (Al_2O_3, EtOAc / *n*-hexane = 1/10) pure **7b** (868 mg, 77%) was obtained as an oil. ^{1}H-NMR: δ 0.81 (t, J=7.6 Hz, 3H, C_6-CH_2CH_3), 1.31 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.72 A of AB (J=9.0 Hz, 1H, H_{10}), 1.93 (q, J=7.6 Hz, 2H, C_6-CH_2), 2.65 B of AB (d, J=9.0 Hz, 1H, H_{10}), 2.86 (br s, 1H, H_7), 3.07 (br s, 1H, H_1), 4.23 (q, J=7 Hz, 2H, OCH_2CH_3), 5.75-5.89 (m, 1H, H_8 or H_9), 5.95-6.16 (m, 1H, H_8 or H_9), 5.96 (d, J=5.9 Hz, 1H, H_4), 7.44 (d, J=5.9 Hz, 1H, H_3); IR (CCl_4): ν 1725, 1710 cm^{-1}; EI/MS: m/e 246 (M^+), 228 (M^+-CO), 145 (M-CO-CO_2Et), 66 (C_5H_6); Found 246.1251. $C_{15}H_{18}O_3$ requires 246.1256.

Ethyl 6-*allyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **7c**

The procedure as described for **7a** was followed. Starting from diisopropylamine (0.59 g, 5.84 mmol), *n*-BuLi (4.0 ml, 6.4 mmol), **1** (1.0 g, 4.59 mmol) and allyl iodide (1.15 g, 6.85 mmol) produced crude **7c** (1.151 g). Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/20) yielded **7c** as an oil (810 mg, 68%) which was contaminated with some **8c**. ^{1}H-NMR: δ 1.28 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.73 A of AB (d, J=9.0 Hz, 1H, H_{10}), 2.58-2.77 (m, 3H, H_{10}, C_6-CH_2), 2.89 (br s, 1H,

H_7), 3.06 (br s, 1H, H_1), 4.16 (q,q, J=7.0 Hz, 2H, diastereotopic OCH_2CH_3), 4.88-5.12 (m, 2H, C_6-CH_2CHCH_2), 5.17-6.13 (m, 4H, H_4, H_8, H_9, C_6-CH_2CHCH_2), 7.40 (d, J=5.8 Hz, 1H, H_3); IR (CCl_4): ν 2980, 1725, 1710, 1590 (C=C, unsat.), 1230, 910 cm^{-1}; EI/MS: m/e 258 (M^+), 230 (M-CO), 157 (M-CO-COOEt), 115, 66 (C_5H_6); Found 258.1251. $C_{16}H_{18}O_3$ requires 258.1256.

Ethyl 6-n-*heptyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **7d**

Diisopropylamine (0.69 g, 6.83 mmol), *n*-BuLi (4.5 ml, 7.2 mmol), **1** (1.20 g, 5.505 mmol) and *n*-heptyl iodide (1.4 g, 6.19 mmol) were reacted according to the procedure described for **7a**, to yield **7d** (810 mg, 47 %) after flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/20, Rf = 0.5) as an oil. ^{1}H-NMR: δ 0.71-1.44 (m, 16H, OCH_2CH_3, C_6-$CH_2C_6H_{13}$), 1.69-1.98 (m, 3H, H_{10}, C_6-CH_2), 2.67 B of AB (d, J=9.4 Hz, 1H, H_{10}), 2.82 (br s, 1H, H_7), 3.02 (br s, 1H, H_1), 4.21 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.87 (dd, J=5.6 Hz, J=2.8 Hz, 1H, H_8 or H_9), 5.95 (d, J=6.0 Hz, 1H, H_4), 6.07 (dd, J=5.6 Hz, J=2.8 Hz, 1H, H_8 or H_9), 7.43 (d, J=6.0 Hz, 1H, H_3); IR (CCl_4): ν 2920, 1727, 1707, 1590, 1228 cm^{-1}; EI/MS: m/e 316 (M^+), 288 (M-CO), 243 (M-COOEt), 189 (M-CO-C_7H_{15}), 117, 66 (C_5H_6); Found 316.2030. $C_{20}H_{28}O_3$ requires 316.2038.

Ethyl 6-*benzyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **7e**

The procedure as described for **7a** was followed. Starting from diisopropylamine (0.22 g, 2.18 mmol), *n*-BuLi (1.33 ml, 2.13 mmol), **1** (0.20 g, 0.917 mmol) and benzyl bromide (0.32 g, 1.87 mmol) furnished 0.27 g of a crude yellow oil which consisted of benzyl bromide, 1,2-diphenylbromoethane, **7e** and **8e**. Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10) gave 1,2-diphenylbromoethane (0.35 mg, Rf = 0.5) and a 1:3 molar mixture of **7e** and its Cope rearranged isomer **8e** (Rf = 0.25, 80 mg, 28 %). These compounds could not be isolated separately due to rapid equilibration. Therefore only the ^{1}H-NMR- and MS-data of **7e** are relevant. **7e**: ^{1}H-NMR: δ 1.07 (t, J=7.0 Hz, 3H, OCH_2CH_3), 5.83-6.15 (m, 3H, H_4, H_8, H_9), 7.04-7.84 (m, 6H, Ph, H_3). The other ^{1}H-absorptions were not distinguishable from those of **8e**. EI/MS: m/e 308 (M^+), 280 (M-CO), 217 (M-benzyl), 117, 91 (benzyl), 66 (C_5H_6); Found 308.1417. $C_{20}H_{20}O_3$ requires 308.1412. 1,2-*Diphenylbromoethane*: ^{1}H-NMR: δ 3.52 (d, J=7.6 Hz, 2H, H_2), 5.13 (t, J= 7.6 Hz, 1H, H_1), 7.10 (s, 5H, Ph), 7.25 (s, 5H, Ph); IR (CCl_4): ν 3030, 1490, 1450 cm^{-1}; EI/MS: m/e 262, 260 (M^+), 181 (M^+-Br; $C_{14}H_{13}^+$); Found 181.1017. $C_{14}H_{13}$ (M^+-Br) requires 181.1018.

Ethyl 6-*iodomethyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **7f**

Diisopropylamine (0.60 g, 5.94 mmol), *n*-BuLi (4.0 ml, 6.4 mmol), **1** (1.00 g, 4.587 mmol) and diiodomethane (1.60 g, 5.97 mmol) were reacted according to the procedure described for **7a** to yield 1.6 g of a mixture which contained **1**, **7f**, **8f** and polymeric material. Conscientious flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10, Rf = 0.2) gave pure **7f** (125 mg, 8 %) as an oil. ^{1}H-NMR: δ 1.36 (t, J=7 Hz, 3H, OCH_2CH_3), 1.64 A of AB (d, J=10.0 Hz, 1H, H_{10}), 1.84 B of AB (d, J=10.0 Hz, 1H, H_{10}), 2.82 (br s, 1H, H_7), 3.18 (br s, 1H, H_1), 3.60 A of AB (d, J=9.3 Hz, 1H, C_6-CH_2), 3.73 B of

AB (d, J=9.3 Hz, 1H, C_6-CH_2), 4.31 (q, J=7 Hz, 2H, OCH_2), 5.85-6.29 (m, 3H, H_4, H_8, H_9), 7.56 (d, J= 6.0 Hz, 1H, H_3); IR (CCl_4): ν 1725 (C=O, ester), 1710 (C=O, enone), 1225 cm^{-1}; CI/MS: m/e 359 (M^++1), 293 (M+1-C_5H_6), 231 (M-I), 203 (M-I-CO), 67 (C_5H_6+1); Found 359.0149. $C_{14}H_{16}IO_3$ requires 359.0144.

Ethyl 7-*methyl*-10-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **8a**

A stirred soln of **7a** (423 mg, 1.823 mmol) in $CHCl_3$ was refluxed for 15 min. After cooling to r.t. a mixture of **7a** and **8a** was obtained (molar ratio = 65:35, the average result of three ^{1}H-NMR measurements). Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/20, Rf = 0.25) yielded pure **8a** (128 mg, 30 %) as an oil. ^{1}H-NMR: δ 1.30 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.48 (s, 3H, C_7-CH_3), 1.80-2.67 (m, 3H, H_5, H_6), 3.22 (t, J=4 Hz, 1H, H_1), 3.43-3.70 (m, 1H, H_2), 4.20 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.24-5.47 (m, 1H, H_3 or H_4), 5.67-5.83 (m, 1H, H_3 or H_4), 7.11 (d, J=4 Hz, 1H, H_9); IR (CCl_4): ν 3060, 2980, 1780 (C=O, bridged), 1710 (C=O, ester), 1270, 1230, 1185, 1085, 1045 cm^{-1}; EI/MS: m/e 232 (M^+), 204 (M-CO), 189 (M-CO-CH_3), 159 (M-COOEt), 131 (M-CO-COOEt), 66 (C_5H_6); Found 232.1090. $C_{14}H_{16}O_3$ requires 232.1099.

Ethyl 7-*ethyl*-10-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **8b**

Ester **7b** (513 mg, 2.085 mmol) was reacted as described for **8a** to produce a mixture of **7b** and **8b** (molar ratio = 35:65 (^{1}H-NMR)). Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/20, Rf = 0.25-0.30) yielded pure **8b** (274 mg, 53 %) as an oil. ^{1}H-NMR: δ 0.97 (t, J=7.4 Hz, 3H, C_7-CH_2CH_3), 1.31 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.62-2.73 (m, 5H, H_5, H_6, C_7-CH_2), 3.21 (t, J≅4 Hz, 1H, H_1), 3.44-3.71 (m, 1H, H_2), 4.22 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.31-5.46 (m, 1H, H_3 or H_4), 5.71-5.84 (m, 1H, H_3 or H_4), 7.11 (d, J=3.8 Hz, 1H, H_9); IR (CCl_4): ν 3050, 2980, 1780 (C=O, bridged), 1710 (C=O, ester), 1575 (C=C, unsat.), 1270, 1180, 1080 cm^{-1}; EI/MS: m/e 246 (M^+), 218 (M-CO), 189, 145 (M-CO-COOEt), 117 (M-CO-COOEt-Et), 66 (C_5H_6); Found 246.1252. $C_{15}H_{18}O_3$ requires 246.1256.

Ethyl 7-*allyl*-10-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **8c**

Ester **7c** (276 mg, 1.070 mmol) was reacted as described for **8a** to produce a mixture of **7c** and **8c** (molar ratio = 40:60 (^{1}H-NMR)). Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/20, Rf = 0.25) yielded pure **8c** (153 mg, 55 %) as an oil. ^{1}H-NMR: δ 1.31 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.16-2.43 (m, 2H, H_5), 2.45-3.11 (m, 3H, H_6, C_7-CH_2), 3.24 (t, J≅4 Hz, 1H, H_1), 3.47-3.71 (m, 1H, H_2), 4.22 (q,q, J=7.0 Hz, 2H, diastereotopic OCH_2CH_3), 4.88-5.28 (m, 2H, C_7-CH_2CHCH_2), 5.33-5.48 (m, 1H, H_3 or H_4), 5.66-6.18 (m, 2H, H_3 or H_4, C_7-CH_2CHCH_2), 7.10 (d, J=3.9 Hz, 1H, H_9); IR (CCl_4): ν 3050, 2980, 1784 (C=O, bridged), 1716 (C=O, ester), 1640 (C=C), 1575 (C=C, unsat.), 1270, 1095 cm^{-1}; EI/MS: m/e 258 (M^+), 230 (M-CO), 157, 115, 66 (C_5H_6); Found 258.1261. $C_{16}H_{18}O_3$ requires 258.1256.

Ethyl 7-n-*heptyl*-10-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **8d**

Ester **7d** (312 mg, 0 99 mmol) was reacted as described for **8a** to produce a mixture of **7d** and **8d** (molar ratio = 35 65 (^{1}H-NMR)) Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/20, Rf = 0 6) yielded pure **8d** (152 mg, 49 %) as an oil ^{1}H-NMR δ 0 71-1 98 (m, 18 H, OCH_2CH_3, C_7-*n*-C_7H_{15}), 1 98-2 73 (m, 3H, H_5, H_6), 3 20 (t, J≅4 Hz, 1H, H_1), 3 40-3 69 (m, 1H, H_2), 4 22 (q, J=7 0 Hz, 2H, OCH_2CH_3), 5 31-5 45 (m, 1H, H_3 or H_4), 5 69 5 83 (m, 1H, H_3 or H_4), 7 11 (d, J=3 8 Hz, 1H, H_9), IR (CCl_4) ν 2920, 1780 (C=O, bridged), 1710 (C=O, ester), 1265, 1090 cm^{-1}, EI/MS m/e 316 (M^+), 288 (M-CO), 189 (M-CO-C_7H_{15}), 117, 66 (C_5H_6), Found 316 2031 $C_{20}H_{28}O_3$ requires 316 2038

Ethyl 7-*benzyl*-10-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **8e**

Ester **8e** was obtained as an equilibrium mixture with **7e** (molar ratio = 25 75 (^{1}H-NMR)) **8e** ^{1}H-NMR δ 1 16 (t, J=7 Hz, 3H, OCH_2CH_3), 2 27-3 67 (m, 7H, H_1, H_2, H_5, H_6, C_7-CH_2), 3 91-4 28 (m, 2H, diastereotopic OCH_2CH_3), 5 28-5 44 (m, 1H, H_3 or H_4), 5 69-5 87 (m, 1H, H_3 or H_4), 7 02 (d, J=3 9 Hz, 1H, H_9), 7 04-7 84 (m, 5H, Ph), IR (CCl_4) ν 1785 (C=O, bridged), 1712 (C=O, ester), 1280 cm^{-1}, EI/MS m/e 308 (M^+), 280 (M-CO), 217 (M-benzyl), 117, 91 (benzyl), 66 (C_5H_6), Found 308 1417 $C_{20}H_{20}O_3$ requires 308 1412

Ethyl 7-*iodomethyl*-10-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **8f**

A mixture of **7f** and **8f** was obtained upon iodomethylation of **1** (*Cf* the synthesis of **7f**) Although complete separation was impossible, **8f** was characterized by its spectral data, ^{1}H-NMR δ 1 36 (t, J=7 Hz, 3H, OCH_2CH_3), 2 00-2 82 (m, 3H, H_5, H_6), 3 22-3 38 (m, 1H, H_1), 3 49 A of AB (d, J=10 Hz, 1H, C_7-CH_2), 3 55-3 78 (m, 1H, H_2), 3 97 B of AB (d, J=10 Hz, 1H, C_7 CH_2), 4 21 (q, J=7 Hz, 2H, OCH_2), 5 34-5 47 (m, 1H, H_3 or H_4), 5 74-5 89 (m, 1H, H_3 or H_4), 7 13 (d, J=3 7 Hz, 1H, H_9), IR (CCl_4) ν 1790 (C=O, bridged), 1710 (C=O, ester), 1270, 1095 cm^{-1}, CI/MS m/e 359 (M^++1), 293 (M+1-C_5H_6), 231 (M-I), 203 (M-I-CO), 67 (C_5H_6+1), Found 359 0149 $C_{14}H_{16}IO_3$ requires 359 0144

Reaction of **7a** *with MeLi*

To a soln of **7a** (480 mg, 2 07 mmol) in dry THF at -78 °C was added MeLi (1 7 ml, 1 6 M soln in Et_2O, 2 72 mmol) using a syringe The mixture was allowed to attain -50 °C and subsequently treated with an excess of HCl (3 % aq), extracted with Et_2O (3 x 25 ml), washed with water (3 x 20 ml), dried and concentrated *in vacuo* The resulting crude oil was further purified by flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10) to yield successively **14**, **15**, **17** and a mixture of **18** and **7a**

6-{2-*(2-Hydroxypropyl)*}-2-*methyl*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-4,8 *dien* 3 *one* **14** (65 mg, 14 %, Rf = 0 10-0 15, Al_2O_3, EtOAc /*n* hexane=1/10) ^{1}H-NMR δ 1 42 (s, 6H, C_2-Me, C_6-C(OH)-(CH_3)CH_3), 1 56 (s, 3H, C_6-C(OH)(CH_3)CH_3), 1 64 A of AB (br d, J≅8 8 Hz, 1H, H_{10}), 2 31 B of AB (br d, J≅8 8 Hz, 1H, H_{10}), 2 67 (br s, 1H, H_1), 3 00 (br s, 2H, H_7, OH), 5 96 (br s, 2H, H_8, H_9), 5 98 (d, J=6 2 Hz, 1H, H_4), 7 40 (d, J=6 2 Hz, 1H, H_5), IR (CCl_4) ν 3620 (OH), 3540-3300 (OH), 2970, 1700 (C=O), 1590 (C=C, unsat) cm^{-1}, EI/MS m/e 218 (M^+), 203 (M-Me), 66 (C_5H_6), Found 218 1284

$C_{14}H_{18}O_2$ requires 218.1307.

Ethyl 7-syn-10-*dimethyl*-anti-10-*hydroxy*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **15** (130 mg, 20 % yield; 80 % purity by CapGC). ^{1}H-NMR: δ 1.13 (s, 3H, C_{10}-Me), 1.24 (t, J=7 Hz, 3H, OCH_2CH_3), 1.27 (s, 3H, C_7-Me), 1.77 (s, 1H, OH), 1.80-2.43 (m, 2H, H_5), 2.60-2.93 (m, 2H, H_1, H_6), 3.50-3.77 (m, 1H, H_2), 4.18 (q, J=7 Hz, 2H, OCH_2), 5.38-5.57 (m, 2H, H_3, H_4), 6.82 (d, J=3.8 Hz, 1H, H_9); IR (CCl_4): ν 3620, 3500 (OH), 3040, 1710, (C=O), 1585 (C=C, unsat.), 1260, 1230, 1060 cm^{-1}; CI/MS: m/e 249 (M^++1), 231 (M+1-H_2O), 217, 203 (M+1-HOEt), 183 (M+1-C_5H_6), 67 (C_5H_6+1); EI/MS: m/e 248 (M^+), 230 (M-H_2O), 202 (M-HOEt), 136 (M-HOEt-C_5H_6); Found 249.1487. $C_{15}H_{21}O_3$ requires 249.1491.

8-*Acetyl*-7-syn-10-*dimethyl*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*dien*-anti-10-*ol* **17** (26 mg, 6 %). M.p. 78-81 °C (after recrystallization from *n*-hexane), ^{1}H-NMR: δ 1.11 (s, 3H, C_{10}-Me), 1.31 (s, 3H, C_7-Me), 1.53-2.42 (m, 3H, H_5, C_{10}-OH), 2.20 (s, 3H, C_8-$COCH_3$), 2.60-2.91 (m, 2H, H_1, H_6), 3.53-3.78 (m, 1H, H_2), 5.34-5.54 (m, 2H, H_3, H_4), 6.76 (d, J=3.9 Hz, 1H, H_9); IR (CCl_4): ν 3620 (OH), 1670 (C=O, unsat.), 1575 (C=C, unsat.) cm^{-1}; EI/MS: m/e 218 (M^+), 175 (M-CH_3CO), 152 (M-C_5H_6), 43 (CH_3CO); Found 218.1301. $C_{14}H_{18}O_2$ requires 218.1307.

The mixture of **18** and **7a** (165 mg, ratio 3:1, ^{1}H-NMR) was separated by repeated (2x) flash chromatography (Al_2O_3, toluene/CH_2Cl_2 = 2/1, Rf = 0.45), to yield 8-*acetyl*-7-*methyl*-endo-*tricyclo*-[5.2.1.$0^{2,6}$]*deca*-3,8-*dien*-10-*one* **18** (45 mg, 11 %) as a pure white solid. M.p. 57-62 °C (after recrystallization from *n*-pentane). ^{1}H-NMR: δ 1.47 (s, 3H, C_7-Me), 2.27 (s, 3H, C_8-$COCH_3$), 1.78-2.56 (m, 3H, H_5, H_6), 3.28 (t, J=4.0 Hz, 1H, H_1), 3.47-3.78 (m, 1H, H_2), 5.34-5.45 (m, 1H, H_3 or H_4), 5.69-5.83 (m, 1H, H_3 or H_4), 7.03 (d, J=4.0 Hz, 1H, H_9); IR (KBr): ν 2920, 1780 (bridged C=O), 1660 (C=O, unsat.), 1560 (C=C, unsat.), 1270 cm^{-1}; EI/MS: m/e 202 (M^+), 174 (M-CO), 159 (M-CH_3CO), 131 (M-CO-CH_3CO^+), 43; Found 202.0990. $C_{13}H_{14}O_2$ requires 202.0944.

8-*(2-(2-Hydroxypropyl))*-7-*methyl*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*dien*-10-*one* **19**

Ester **14** (42 mg, 0.19 mmol) was refluxed in $CHCl_3$ for 15 min to afford an equilibrium mixture of **14** and **19** (ratio 1:1 (^{1}H-NMR)). This mixture was separated by flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/3, Rf = 0.2-0.25) to give **19** (15 mg, 36 %) as a pure oil. ^{1}H-NMR: δ 1.42 (s, 6H, C_8-$C(CH_3)_2$), 1.48 (s, 3H, C_7-CH_3), 2.29-2.60 (m, 3H, H_5, H_6), 3.01 (t, J=4.1 Hz, 1H, H_1), 3.33-3.62 (m, 2H, H_2, OH), 5.28-5.45 (m, 1H, H_3 or H_4), 5.67-5.85 (m, 1H, H_3 or H_4), 6.03 (d, J=4.1 Hz, 1H, H_9); IR (CCl_4): ν 3620 (OH), 2930, 1775 (bridged C=O) cm^{-1}; EI/MS: m/e 218 (M^+), 200 (M-H_2O), 190 (M-CO), 172 (M-CO-H_2O), 59 (($CH_3)_2COH^+$); Found 218.1280. $C_{14}H_{18}O_2$ requires 218.1307.

Nucleophilic epoxidation of **7a**

To a vigorously stirred soln of **7a** (2.0 g, 8.62 mmol) in MeOH (20 ml)/CH_2Cl_2 (20 ml) was added H_2O_2 (10 ml, 40 % aq) and NaOH (14 ml, 0.2 N). The temperature was raised to 65 °C and both H_2O_2 (10 ml, 40 % aq.) and NaOH (14 ml, 0.2 N) were added repeatedly after 30, 90 and 150 min reaction time, respectively. After 6 h the reaction mixture was allowed to attain r.t.. The organic layer was

separated and the water layer was extracted with $CHCl_3$ (3 x 50 ml). The combined organic layers were washed with water (3 x 10 ml), dried and evaporated *in vacuo*. *Ca.* 50 % of **7a** had reacted (^{1}H-NMR). Two successive flash chromatographic purification steps (silica gel, EtOAc /*n*-hexane = 1/5, Rf = 0.25) yielded *ethyl* exo-3,4-*epoxy*-6-*methyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*ene* 2-*carboxylate* **20** (0.66 g, 31 %) as a viscous oil which slowly solidified (m.p. 49-56 °C). ^{1}H-NMR: δ 1.18-1.47 (m, 5H, H_{10}, OCH_2CH_3), 1.58 (s, 3H, C_6-Me), 2.70-2.87 (m, 1H, H_7), 3.08-3.22 (m, 1H, H_1), 3.33 (d, J=2.4 Hz, 1H, H_3), 3.79 (d, J=2.4 Hz, 1H, H_4), 4.27 (q, J=7.0 Hz, 2H, OCH_2CH_3), 6.01-6.27 (m, 2H, H_8, H_9); IR (CCl_4): ν 2980, 1744 (C=O), 1235, 910 cm^{-1}; EI/MS: m/e 248 (M^+), 233 (M-CH_3), 183 (M-$C_5H_6^+$), 66 (C_5H_6); Found 248.1054. $C_{14}H_{16}O_4$ requires 248.1049; Found C, 67.28; H, 6.48. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50.

During the aforementioned separation also a small amount of **21** (260 mg, 75 % purity by CapGC) was isolated. **21** was purified by flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/5, Rf = 0.5) which finally gave 0.051 g (2 %) pure white solid. Ester **21** was also prepared[14] by dissolving **8a** (175 mg, 0.754 mmol) in HOAc (2.2 ml), adding H_2O_2 (0.2 g, 35 % aq, 2.06 mmol) and stirring for 20 h at 4 °C. After extraction with Et_2O (3 x 50 ml), washing with $NaHCO_3$ (10 % aq), drying and concentrating *in vacuo*, pure *ethyl* 7-*methyl*-11-*oxo*-endo-10-*oxatricyclo*[5.2.2.$0^{2,6}$]*undeca*-3,8-*diene* 8-*carboxylate* **21** (115 mg, 61 %) was isolated as a white solid. M.p. 94-97 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.29 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.84 (s, 3H, C_7-Me), 2.00-2.20 (m, 1H, H_5), 2.29-2.73 (m, 1H, H_5), 2.91 (ddd, J≅9.6 Hz, J≅8.4 Hz, J=4.0 Hz, 1H, H_6), 3.31-3.57 (m, 1H, H_2), 3.67 (dd, J=6.4 Hz, J=3.0 Hz, 1H, H_1), 4.20 (q, J=7.2 Hz, 2H, OCH_2), 5.34-5.49 (m, 1H, H_3 or H_4), 5.53-5.70 (m, 1H, H_3 or H_4), 7.14 (d, J=6.4 Hz, 1H, H_9); IR (KBr): ν 1750, 1725, 1710 (C=O), 1615 (C=C), 1265, 1075 cm^{-1}; EI/MS: m/e 249 (M^++1), 204 (M-CO_2), 183 (M-$C_5H_6^+$), 131 (M-CO_2-COOEt), 66 (C_5H_6); Found C, 67.25; H, 6.57. $C_{14}H_{16}O_4$ requires C, 67.73; H, 6.50.

Ethyl syn-10-*cyano*-anti-10-*hydroxy*-7-*methyl*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **23**

Ester **7a** (1.00 g, 4.31 mmol), KCN (560 mg, 8.60 mmol) and NH_4Cl (390 mg, 7.29 mmol) were added to a mixture of DMF (20 ml)/H_2O (10 ml) and stirred for 15 h at 40 °C. Excess AcOH (5 ml) and Et_2O (50 ml) were added, and the resulting mixture was thoroughly washed with water (8 x 5 ml) to remove DMF, dried and concentrated to afford **23** (1.09 g, 98 %). Crystallization from *n*-hexane gave an analytically pure sample; m.p. 92-93 °C. **23** was also synthesized starting from **8a** (33 mg, 0.142 mmol). After stirring for 1 h at r.t., pure **23** (37 mg, 99 %) was obtained. ^{1}H-NMR: δ 1.32 (t, J=7 Hz, 3H, OCH_2CH_3), 1.58 (s, 3H, C_7-Me), 1.71-2.53 (m, 2H, H_5), 2.60-2.98 (m, 1H, H_6), 3.20 (t, J=3.8 Hz, 1H, H_1), 3.38-3.83 (m, 2H, H_2, OH), 4.21 (q, J=7 Hz, 2H, OCH_2), 5.36-5.65 (m, 2H, H_3, H_4), 6.88 (d, J=3.8 Hz, 1H, H_9); IR (KBr): ν 3400 (OH), 1680 (C=O, unsat.), 1585 (C=C, unsat.), 1060 cm^{-1}; CI/MS: m/e 260 (M^++1), 242 (M+1-H_2O), 233 (M-CN), 187 (M+1-COOEt), 66 (C_5H_6); UV (MeOH): λ_{max} 224 nm, (6500); MS: Found 260.1280. $C_{15}H_{18}O_3N$ requires 260.1287; Found C, 69.12; H, 6.54; N, 5.37. $C_{15}H_{17}O_3N$ requires C, 69.48; H, 6.61; N, 5.40.

Ethyl anti-10-*acetoxy*-syn-10-*cyano*-7-*methyl*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca* 3,8 *diene* 8 *carboxylate* **24**

Alcohol **23** (1 09 g, 4 209 mmol) was added to a mixture of Ac_2O (3 0 g, 29 4 mmol) in pyridine (10 ml) and stirred for 40 h at r t Excess of $NaHCO_3$ aq was added After extraction with Et_2O (3 x 30 ml), the combined organic layers were washed with water (5 x 10 ml), dried and concentrated to yield pure **24** (1 10 g, 85 %) M p 123-125 °C (after recrystallization from *n*-hexane /EtOAc = 10/1) ^{1}H NMR δ 1 34 (t, J=7 Hz, 3H, OCH_2CH_3), 1 65 (s, 3H, C_7-Me), 1 70-2 58 (m, 5H, H_5, OAc), 2 67-2 96 (m, 1H, H_6), 3 20-3 49 (m, 1H, H_2), 3 80 (t, J=3 8 Hz, 1H, H_1), 4 21 (q, J=7 Hz, 2H, OCH_2), 5 33-5 47 (m, 1H, H_3 or H_4), 5 51-5 67 (m, 1H, H_3 or H_4), 6 84 (d, J=4 0 Hz, 1H, H_9), ^{13}C-NMR δ 12 3 (q, OCH_2CH_3), 13 9 (q, C_7-CH_3), 20 4 (q, $OCOCH_3$), 32 5 (t, C_5), 43 9 (d, C_6), 50 5 (d), 51 7 (d, C_1, C_2), 60 1 (s, C_7), 60 3 (t, OCH_2), 87 8 (s, C_{10}), 116 5 (s, CN), 127 6 (d), 134 7 (d, C_3, C_4), 137 3 (s, C_8), 143 6 (d, C_9), 163 4 (s, C_8-CO), 168 5 (q, J=3 6 Hz, $OCOCH_3$), IR (KBr) ν 2245 (CN), 1755 (C=O, acetate), 1705 (C=O), 1590 (C=C, unsat), 1370, 1220 cm^{-1}, CI/MS m/e 302 (M^++1), 256 (M+1-HOEt), 242 (M+1-HOAc), 67 (C_5H_6+1), UV (MeOH) λ_{max} 219 nm, (6000), Found C, 67 93, H, 6 46, N, 4 63 $C_{17}H_{19}O_4N$ requires C, 67 76, H, 6 36, N, 4 65

Cu(I)-catalyzed Grignard addition of MeMgI to **7a**

Mg (50 mg, 2 06 mmol) was added to dry Et_2O (10 ml) in a N_2 atmosphere at 0 °C Then MeI (300 mg, 2 11 mmol) in Et_2O was added using a syringe The resulting mixture was stirred for 30 min and oven dried Cu(I)Cl (12 mg, 0 12 mmol) was added After addition of **7a** (363 mg, 1 565 mmol) in Et_2O (10 ml), stirring was continued for 4 h The reaction mixture was allowed to attain r t and stirred for another 15 h An excess of NH_4Cl aq was added After extraction with Et_2O (3 x 30 ml), the combined organic layers were washed with water (5 x 10 ml), dried and concentrated, to yield a 3 2 molar mixture of **15** and **7a** (360 mg, ^{1}H-NMR) Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/5) finally gave pure **15** (122 mg, 31 %) and **7a** (185 mg, 51 %)

Reaction of **8a** *with MeLi*

To a soln of **8a** (100 mg, 0 431 mmol) in dry Et_2O at -78 °C was added MeLi (0 41 ml, 1 6 M soln in *n* hexane, 0 66 mmol) using a syringe After stirring for 10 min at -78 °C, an excess of HCl (3 % aq) was added and the mixture was allowed to attain r t , extracted with Et_2O (3 x 25 ml), washed with H_2O (3 x 10 ml), dried ($MgSO_4$) and concentrated *in vacuo* The crude product was purified by flash chromatography (Al_2O_3, EtOAc /*n* hexane = 1/10, Rf = 0 10-0 15) to yield **15** as a pure oil (89 mg, 83 %, 99 % purity by CapGC)

Ethyl anti-10-*acetoxy*-7-syn-10-*dimethyl* endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **25**

Alcohol **15** (100 mg, 0 403 mmol) was dissolved in an excess of Et_3N (1 0 g, 9 90 mmol)/CH_2Cl_2 (5 ml) After addition of an excess of Ac_2O (0 5 g, 4 90 mmol) and DMAP (96 mg, 0 76 mmol), the

resulting mixture was stirred for 5 h at r.t and worked up as described for the preparation of **24**, to afford crude **25** (150 mg). Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10, Rf = 0.5) gave pure **25** (90 mg, 77 %). M.p. 87-88 °C (after recrystallization from *n*-pentane). ^{1}H-NMR: δ 1.28 (t, J=7 Hz, 3H, OCH_2CH_3), 1.28 (s, 3H, C_7-Me), 1.37 (s, 3H, C_{10}-Me), 1.69-2.47 (m, 5H, H_5, OAc), 2.81 (ddd, J=9.4 Hz, J=8 Hz, J=4 Hz, 1H, H_6), 3.16-3.42 (m, 1H, H_2), 3.57 (t, J≅4 Hz, 1H, H_1), 4.18 (q, J=7 Hz, 2H, OCH_2), 5.31-5.60 (m, 2H, H_3, H_4), 6.81 (d, J=3.8 Hz, 1H, H_9); IR (KBr): ν 2900, 1737 (C=O, acetate), 1706 (C=O), 1595 (C=C, unsat.) cm^{-1}; EI/MS: m/e 290 (M^+), 245 (M-OEt^+), 230 (M-HOAc), 224 (M-C_5H_6), 182, 108; Found 290.1515. $C_{17}H_{22}O_4$ requires 290.1518. Found C, 70.13; H, 7.66. $C_{17}H_{22}O_4$ requires C, 70.32; H, 7.64.

Ethyl anti-10-*hydroxy*-7-*methyl*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **26**

Ester **8a** (200 mg, 0.862 mmol) was dissolved in EtOH (10 ml) and $NaBH_4$ (101 mg, 2.67 mmol) was added. The resulting mixture was stirred for 30 min at r.t. The soln was successively acidified with HCl (1 % aq), washed with $NaHCO_3$ aq, extracted twice with Et_2O and concentrated, to produce crude **26** (189 mg). After flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1, Rf = 0.4) pure **26** (130 mg, 64 %) was isolated as an oil. ^{1}H-NMR: δ 1.27 (t, J=7 Hz, 3H, OCH_2CH_3), 1.41 (s, 3H, C_7-Me), 1.71-2.93 (m, 5H, H_1, H_5, H_6, C_{10}-OH), 3.40-3.71 (m, 2H, H_2, H_{10}), 4.16 (q, J=7 Hz, 2H, OCH_2), 5.48 (m, 2H, H_3, H_4), 6.79 (d, J=3.8 Hz, 1H, H_9); IR (CCl_4): ν 3620 (OH), 1710 (C=O), 1585 (C=C, unsat.), 1050 cm^{-1}; EI/MS: m/e 234 (M^-); Found 234.1245. $C_{14}H_{18}O_3$ requires 234.1256.

Ethyl anti-10-*acetoxy*-7-*methyl*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **27**

Alcohol **26** (123 mg, 0.53 mmol) was acylated as described for the preparation of **24**, using Ac_2O (0.51 g, 5.0 mmol), pyridine (2 ml) and CH_2Cl_2 (10 ml) to give crude **27** (145 mg). Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3, Rf = 0.4) afforded pure **27** (126 mg, 87 %) as an oil. ^{1}H-NMR: δ 1.20 (t, J=7 Hz, 3H, OCH_2CH_3), 1.33 (s, 3H, C_7-Me), 1.71-2.40 (m, 5H, H_5, OAc), 2.65 (ddd, J=9 Hz, J=8 Hz, J=4 Hz, 1H, H_6), 2.96 (td, J=3.8 Hz, J=1.6 Hz, 1H, H_1), 3.29-3.58 (m, 1H, H_2), 4.09 (q, J=7 Hz, 2H, OCH_2), 4.30 (d, J=1.6 Hz, 1H, H_{10}), 5.34-5.65 (m, 2H, H_3, H_4), 6.77 (d, J=3.8 Hz, 1H, H_9); IR (CCl_4): ν 1740 (C=O, acetate), 1710 (C=O), 1590 (C=C, unsat.), 1235, 1040 cm^{-1}; EI/MS: m/e 276 (M^+), 216 (M-HOAc), 210 (M-C_5H_6), 168; Found 276.1363. $C_{16}H_{20}O_4$ requires 276.1362.

6-*Methyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylic acid* **29**

Ester **7a** (0.528 g, 2.276 mmol) was added to a stirred soln of 10 % methanolic NaOH and the resulting mixture was stirred for 1.5 h at r.t. After removal of MeOH *in vacuo*, water (20 ml) was added and the mixture was extracted twice with Et_2O. The aqueous residue was acidified by addition of HCl (20 % aq) and extracted with Et_2O (3 x 50 ml), washed with water (2 x 20 ml), dried and concentrated *in vacuo* to yield pure **29** (0.446 g, 96 %) as a white-yellow solid. ^{1}H-NMR (CD_3COCD_3): δ 1.29 (s, 3H, C_6-Me), 1.69 (dt, ^{2}J=9.0 Hz, J=1.6 Hz, 1H, H_{10}), 2.43 (d, ^{2}J=9.0 Hz, 1H,

H_{10}), 2.62-2.73 (m, 1H, H_7), 3.11-3.22 (m, 1H, H_1), 5.93 (d, J=5.9 Hz, 1H, H_4), 5.96 (s, 2H, H_8, H_9), 5.32-6.22 (br s, 1H, C_2-COOH), 7.48 (d, J=5.9 Hz, 1H, H_3); IR (KBr): ν 1732 (C=O, acid), 1668 (C=C), 1580 (C=C, unsat.), 1220 cm^{-1}; EI/MS: m/e 204 (M^+), 176 (M-CO), 161 (M-CO-Me), 66 (C_5H_6); Found 204.0781. $C_{12}H_{12}O_3$ requires 204.0786.

Thermal fragmentation of **29** *in DMF*

A stirred soln of **29** (100 mg, 0.49 mmol) in DMF (5 ml) was heated at 150 °C for 2.5 h in a N_2 atmosphere. The reaction mixture was then allowed to cool and most of the DMF was removed *in vacuo*, Et_2O (50 ml) was added and the organic layer was thoroughly washed with water (8 x 5 ml) to remove the remaining DMF. After drying ($MgSO_4$) and concentration *in vacuo* a mixture of 2,7-*dimethyl*-1-*oxo*-*indane* 6-*carboxylic acid* **31** and 4-*methyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 3-*carboxylic acid* **32** (86 mg crude yield) was obtained in a molar ratio of 2:1 (^{1}H-NMR). Flash chromatography (silica gel, acetone) gave pure **31** as a viscous oil (17 mg, 17 %). ^{1}H-NMR: δ 1.31 (d, J=7.0 Hz, 3H, C_2-Me), 2.60-2.85 (m, 2H, H_2, H_3), 2.98 (s, 3H, C_7-Me), 3.38 (dd, ^{2}J=18.7 Hz, ^{3}J=9.4 Hz, 1H, H_3), 7.34 (d, J=7.9 Hz, 1H, H_4), 8.18 (d, J=7.9 Hz, 1H, H_5), 8.50-9.14 (br s, 1H, C_6-COOH); IR (CCl_4): ν 3500-2500 (COOH), 2950, 2930, 1710 (C=O, acid), 1600, 1580 (C=C, unsat.) cm^{-1}; EI/MS: m/e 204 (M^+), 189 (M-CH_3), 158, 115, 91 (benzyl), 77; CI/MS: m/e 205 (M^++1); Found 204.0791. $C_{12}H_{12}O_3$ requires 204.0786. These carboxylic acids **31** and **32** were further characterized as their methyl esters. Esterification of a mixture of **31** and **32** with CH_2N_2 (0.3 M soln in Et_2O) in CH_2Cl_2 for 15 min at r.t. quantitatively converted them into a 2:1 mixture of the corresponding methyl esters: *methyl* 2,7-*dimethyl*-1-*oxoindane* 6-*carboxylate* (^{1}H-NMR: δ 1.27 (d, J=7 Hz, 3H, C_2-Me), 2.49-2.87 (m, 2H, H_2, H_3), 2.89 (s, 3H, C_7-Me), 3.35 (dd, ^{2}J=19 Hz, ^{3}J=9 Hz, 1H, H_3), 3.93 (s, 3H, OMe), 7.30 (d, J=7.9 Hz, 1H, H_4), 8.01 (d, J=7.9 Hz, 1H, H_5); CapGC/EI/MS: m/e 218 (M^+), 203 (M-CH_3), 187 (M-OMe), 159 (M-COOMe), 115, 91 (benzyl), 77; Found 218.0941. $C_{13}H_{14}O_3$ requires 218.0943) and *methyl* 4-*methyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 3-*carboxylate* (^{1}H-NMR: δ 1.55-1.82 (m, 2H, H_{10}), 1.91 (d, ^{4}J=1.8 Hz, 3H, C_4-Me), 2.82-2.98 (m, 1H, H_6), 3.11-3.27 (m, 2H, H_1, H_7), 3.40-3.57 (m, 1H, H_2), 3.84 (s, 3H, OMe), 5.64-5.98 (m, 2H, H_8, H_9); CapGC/EI/MS: m/e 218 (M^+), 159 (M-COOEt), 66 (C_5H_6)).

Thermal fragmentation of **7a** *in DMF*

Ester **7a** (286 mg, 1.23 mmol) was dissolved in DMF (5 ml) and heated, while stirring, at 155 °C in a N_2 atmosphere. After work-up (see 'Thermal fragmentation of **29** in DMF'), a mixture containing **34a** and **37** was obtained (molar ratio 1:2, ^{1}H-NMR) that could not be separated by chromatographic means. Therefore, **37** and **34a** were synthesized independently by the two following procedures:

Preparation of **37**: A stirred soln of **35** (24 mg, 0.072 mmol) was heated in DMF at 155 °C for 10 min. Flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10) gave pure **37** (20 mg, 91 %) as an oil. *Diethyl* 2,4-*dimethyl*-3-*oxo*-*indane* 1,5-*dicarboxylate* **37**: ^{1}H-NMR: δ 1.22-1.50 (m, 9H, C_2-Me, 2xOCH_2CH_3), 2.90 (s, 3H, C_4-Me), 2.93-3.28 (m, 1H, H_2), 3.78 (d, J=4.7 Hz, 1H, H_1), 4.28 (q, J=7

Hz, 2H, C_1-COOC**H**$_2$), 4.39 (q, J=7 Hz, 2H, C_5-COOC**H**$_2$), 7.51 (d, J=8.2 Hz, 1H, H_7), 8.04 (d, J=8.2 Hz, 1H, H_6); IR (CCl_4): ν 1730 (C=O), 1600, 1182 cm^{-1}; EI/MS: m/e 304 (M^+), 276 (M-CO), 231 (M-COOEt), 203 (M-CO-COOEt), 175 (M-2CO-COOEt); Found 304.1317. $C_{17}H_{20}O_5$ requires 304.1311.

Preparation of **34a**: A soln of **7a** (900 mg, 3.879 mmol) and cyclopentadiene (7 ml) in DMF was heated at 155 °C for 2.5 h. After cooling to 140 °C most of the cyclopentadiene was removed by blowing through N_2. Subsequently, the mixture was cooled to 50 °C and the DMF was removed *in vacuo*. The resulting crude **34a** was separated by flash chromatography (Al_2O_3, gradient: *n*-hexane to EtOAc /*n*-hexane = 1/20; Rf = 0.3, EtOAc /*n*-hexane = 1/20) from the remaining cyclopentadiene dimers (Rf = 0.8, purple spots with 25 % aqueous H_2SO_4 spray) to produce pure **34a** (708 mg, 79 %) as an oil. *Ethyl* 4-*methyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 3-*carboxylate* **34a**: ^{1}H-NMR: δ 1.37 (t, J=7.1 Hz, 3H, OCH$_2$C**H**$_3$), 1.62 A of AB (d, J=9.0 Hz, 1H, H_{10}), 1.77 (dt, ^{2}J =9.0 Hz, J=1.6 Hz, 1H, H_{10}), 1.91 (d, ^{4}J=1.8 Hz, 3H, C_4-Me), 2.90 (t, J=5.1 Hz, 1H, H_6), 3.09-3.31 (m, 2H, H_1, H_7), 3.40-3.60 (m, 1H, H_2), 4.31 (q, J=7.1 Hz, 2H, OC**H**$_2$CH$_3$), 5.76 (dd, ^{3}J=5.5 Hz, ^{4}J=3.0 Hz, 1H, H_8 or H_9), 5.91 (dd, ^{3}J=5.5 Hz, ^{4}J=3.0 Hz, 1H, H_8 or H_9); ^{13}C-NMR: δ 8.9 (q, C_3-COOCH$_2$**C**H$_3$), 13.9 (q, C_4-Me), 44.4 (d), 44.6 (d), 45.4 (d), 50.2 (d, C_1, C_2, C_6, C_7), 52.0 (t, C_{10}), 60.9 (t, C_3-COO**C**H$_2$), 132.9 (d, C_8, C_9), 150.2 (s), 155.1 (s, C_3, C_4), 165.9 (s, C_3-CO), 210.8 (s, C_5); IR (CCl_4): ν 2990, 2940, 1709 (C=O, ester), 1210 cm^{-1}; EI/MS: m/e 232 (M^+), 158 (M-CO-HOEt), 131 (M-CO-COOEt), 66 (C_5H_6); Found 232.1097. $C_{14}H_{16}O_3$ requires 232.1099.

Ethyl 4-*ethyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 3-*carboxylate* **34b**

The procedure for the synthesis of **34a** was followed, using **7b** (236 mg, 0.959 mmol) and an excess of cyclopentadiene (3.0 ml) in DMF (15 ml). After heating for 1 h, the usual work-up and flash chromatography (Al_2O_3, gradient: *n*-hexane to EtOAc /*n*-hexane = 1/20; Rf = 0.25, EtOAc /*n*-hexane = 1/20) pure **34b** (190 mg, 81 %) was obtained as an oil. ^{1}H-NMR: δ 0.94 (t, J=7.4 Hz, 3H, C_4-CH$_2$C**H**$_3$), 1.37 (t, J=7.0 Hz, 3H, OCH$_2$C**H**$_3$), 1.62 A of AB (d, ^{2}J=8.7 Hz, 1H, H_{10}), 1.78 (dt, ^{2}J =8.7 Hz, J=1.5 Hz, 1H, H_{10}), 2.40 (q, J=7.4 Hz, 2H, C_4-CH$_2$), 2.87 (dd, J=5.7 Hz, J=4.8 Hz, 1H, H_6), 3.09-3.33 (m, 2H, H_1, H_7), 3.52 (t, J=4.8 Hz, 1H, H_2), 4.31 (q, J=7.0 Hz, 2H, OC**H**$_2$CH$_3$), 5.75 (dd, ^{3}J=5.4 Hz, ^{4}J=2.8 Hz, 1H, H_8 or H_9), 5.93 (dd, ^{3}J=5.4 Hz, ^{4}J=2.8 Hz, 1H, H_8 or H_9); ^{13}C-NMR: δ 12.7 (q, C_4-CH$_2$**C**H$_3$), 13.9 (q, C_3-COOCH$_2$**C**H$_3$), 17.2 (t, C_4-**C**H$_2$), 44.7 (d), 45.0 (d), 45.4 (d), 50.2 (d, C_1, C_2, C_6, C_7), 52.2 (t, C_{10}), 60.8 (t, C_3-COO**C**H$_2$), 132.8 (d, C_8, C_9), 154.8 (s), 155.6 (s, C_3, C_4), 165.7 (s, C_3-CO), 210.8 (s, C_5); IR (CCl_4): ν 2960, 1708 (C=O, ester), 1205 cm^{-1}; EI/MS: m/e 246 (M^+), 66 (C_5H_6); Found 246.1250. $C_{15}H_{18}O_3$ requires 246.1256.

Ethyl 4-*allyl*-5-*oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 3-*carboxylate* **34c**

A mixture of **7c** (206 mg, 0.798 mmol) and cyclopentadiene (3.0 ml) in DMF (15 ml) was reacted as described for **34b** to yield **34c** (176 mg, 85 %) as a pure oil after flash chromatography (Al_2O_3, gradient: *n*-hexane to EtOAc /*n*-hexane = 1/20; Rf = 0.30, EtOAc /*n*-hexane = 1/20). ^{1}H-NMR: δ 1.37

(t, J=7.0 Hz, 3H, OCH_2CH_3), 1.62 A of AB (d, ^{2}J=9.2 Hz, 1H, H_{10}), 1.78 (dt, ^{2}J=9.2 Hz, J=1.6 Hz, 1H, H_{10}), 2.91 (t, J=4.8 Hz, 1H, H_6), 3.08-3.38 (m, 4H, H_1, H_7, C_4-CH_2), 3.53 (dd, J=4.8 Hz, J=4.4 Hz, 1H, H_2), 4.31 (q, J=7.0 Hz, 2H, OCH_2CH_3), 4.87-5.16 (m, 2H, C_4-CH_2CHCH_2), 5.49-6.00 (m, 3H, H_8, H_9, C_4-CH_2CH); ^{13}C-NMR: δ 13.7 (q, C_3-$COOCH_2CH_3$), 27.7 (t, C_4-CH_2), 44.6 (d), 44.8 (d), 45.6 (d), 50.1 (d, C_1, C_2, C_6, C_7), 51.8 (t, C_{10}), 60.8 (t, C_3-$COOCH_2$), 116.0 (C_4-CH_2CHCH_2), 132.8 (d), 133.0 (d), 133.9 (d, C_8, C_9, C_4-CH_2CH), 151.0 (s), 155.8 (s, C_3, C_4), 165.4 (s, C_3-CO), 209.8 (s, C_5); IR (CCl_4): ν 2980, 1710 (C=O, ester), 1635 (C=C), 1195 cm^{-1}; EI/MS: m/e 258 (M^+), 66 (C_5H_6); Found 258.1266. $C_{16}H_{18}O_3$ requires 258.1256.

Ethyl 4-n-*heptyl*-5-*oxo*-endo-*tricyclo*[5.2.1.0^{2,6}]*deca*-3,8-*diene* 3-*carboxylate* **34d**

A mixture of **7d** (650 mg, 2.06 mmol) and cyclopentadiene (4 ml) in DMF (15 ml) was reacted as described for **34b** to afford **34d** (530 mg, 82 %) as a pure oil after flash chromatography (2xAl_2O_3, gradient: *n*-hexane to EtOAc /*n*-hexane = 1/20; Rf = 0.50, EtOAc /*n*-hexane = 1/20). ^{1}H-NMR: δ 0.73-1.37 (m, 13H, C_4-$CH_2(CH_2)_5CH_3$), 1.38 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.60 A of AB (d, ^{2}J=8.5 Hz, 1H, H_{10}), 1.78 B of AB (d, ^{2}J =8.5 Hz, 1H, H_{10}), 2.27-2.49 (m, 2H, C_4-CH_2), 2.87 (t, J=4.8 Hz, 1H, H_6), 3.20 (br s, 2H, H_1, H_7), 3.51 (t, J=4.8 Hz, 1H, H_2), 4.31 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.69-5.84 (m, 1H, H_8 or H_9), 5.85-5.96 (m, 1H, H_8 or H_9); IR (CCl_4): ν 2920, 1708 (C=O, ester), 1220, 1107 cm^{-1}; EI/MS: m/e 316 (M^+), 66 (C_5H_6); Found 316.2034. $C_{20}H_{28}O_3$ requires 316.2038.

Ethyl 4-*benzyl*-5-*oxo*-endo-*tricyclo*[5.2.1.0^{2,6}]*deca*-3,8-*diene* 3-*carboxylate* **34e**

A mixture of **7e**/**8e** (25 mg, 0.081 mmol) and cyclopentadiene (1 ml) in DMF (5 ml) was reacted as described for **34b** to furnish **34e** (16 mg, 64 %, 98 % purity by CapGC) after flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/20, Rf = 0.25). ^{1}H-NMR: δ 1.34 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.61 A of AB (d, J=8.4 Hz, 1H, H_{10}), 1.76 (dt, ^{2}J =8.4 Hz, J=1.8 Hz, 1H, H_{10}), 2.88 (t, J=5.0 Hz, 1H, H_6), 3.11-3.33 (m, 2H, H_1, H_7), 3.53 (t, J=5.0 Hz, 1H, H_2), 3.76 (s, 2H, C_4-CH_2), 4.30 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.60-5.87 (m, 2H, H_8, H_9), 7.18 (s, 5H, Ph); IR (CCl_4): ν 1710 (C=O, ester), 1230 cm^{-1}; EI/MS: m/e 308 (M^+), 242, 196, 91 ($PhCH_2^+$), 66 (C_5H_6); Found 308.1414. $C_{20}H_{20}O_3$ requires 308.1412.

Ethyl tetracyclo[9.2.1.0^{2,10}.0^{5,9}]*tetradeca*-3,7,12-*triene* 3-*carboxylate* **39**

A soln of **1** (450 mg, 2.064 mmol) and cyclopentadiene (2 ml) in DMF (10 ml) was heated at 160 °C for 16 h. After removal of DMF and cyclopentadiene at 50 °C *in vacuo*, flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10, Rf = 0.35) gave crude **39** (360 mg). Repeating this purification twice (Al_2O_3, EtOAc /*n*-hexane = 1/20) afforded **39** (209 mg, 34 %, 88 % purity by CapGC). ^{1}H-NMR: δ 1.26 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.55-2.00 (m, 2H, H_{14}), 2.24-3.06 (m, 7H, H_1, H_5, H_6, H_9, H_{10}, H_{11}), 3.26 (br s, 1H, H_2), 4.16 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.33-5.60 (m, 4H, H_7, H_8, H_{12}, H_{13}), 7.07 (dd, J=6.8 Hz, J=1.6 Hz, 1H, H_4); IR (CCl_4): ν 3050, 2920, 1706 (C=O, ester), 1625 (C=C), 1230 cm^{-1}; EI/MS: m/e 256 (M^+), 190 (M-C_5H_6), 117 (M-C_5H_6-COOEt), 66 (C_5H_6); Found 256.1467.

$C_{17}H_{20}O_2$ requires 256.1463.

Flash Vacuum Thermolysis (FVT) of **7a**

FVT of **7a** (572 mg, 2.466 mmol) was carried out as described in the appendix at the end of this Chapter [sample temp.: 60-70 °C, oven temp.: 450 °C, cold trap temp.: -78 °C and p: 4.10^{-2} torr] to afford a mixture of **35** and **40** (378 mg) in a molar ratio of 2.4:1 (^{1}H-NMR) together with a small amount of a regioisomer of **35** (8 %, according to CapGC/MS). Crystallization from *n*-hexane gave *diethyl* 4,7-*dimethyl*-5,10-*dioxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 3,8-*dicarboxylate* **35** (103 mg) as an analytically pure solid. M.p. 77-79 °C; ^{1}H-NMR: δ 1.27 (t, J=7.0 Hz, 3H, C_8-COOCH$_2$CH$_3$), 1.39 (t, J= 7.0 Hz, 3H, C_3-COOCH$_2$CH$_3$), 1.70 (s, 3H, C_7-CH$_3$), 2.00 (s, 3H, C_4-CH$_3$), 2.63 (d, J=5.7 Hz, 1H, H_6), 3.55-3.81 (m, 2H, H_1, H_2), 4.17 (q, J= 7.0 Hz, 2H, C_8-COOCH$_2$CH$_3$), 4.34 (q, J=7 Hz, 2H, C_3-COOCH$_2$CH$_3$), 7.00 (d, J=3.6 Hz, 1H, H_9); IR (CCl_4): ν 1790 (C=O, bridged), 1720 (C=O), 1365, 1270, 1210, 1070 cm^{-1}; CI/MS: m/e 333 (M^++1), 259 (M-COOEt), 167 (M+1-$C_9H_{10}O_3$); Found 333.1343. $C_{18}H_{21}O_6$ requires 333.1338; Found C, 64.95; H, 6.00. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.07. Subsequent flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3) of the remaining mother liquor gave another crop of **35** (142 mg, total yield 30 %) and **40** (90 mg, 18 %). **40** was also prepared by the following procedure: A soln of **21** (80 mg, 0.322 mmol) in DMF (10 ml) was heated for 10 min at 155 °C. After cooling and removal of DMF *in vacuo*, the residue was taken up in Et_2O , thoroughly washed with water (8 x 5 ml), dried and concentrated to afford pure *ethyl* 7-*methyl*-cis-3*a*,7*a*-*dihydroindene* 6-*carboxylate* **40** (57 mg, 87 %). ^{1}H-NMR: δ 1.31 (t, J=7.1 Hz, 3H, OCH$_2$CH$_3$), 2.19 (s, 3H, C_7-Me), 2.24-2.51 (m, 1H, H_1), 2.64-3.11 (m, 2H, H_1, H_{7a}), 3.40-3.69 (m, 1H, H_{3a}), 4.21 (q, J=7.1 Hz, 2H, OCH$_2$), 5.40 (dd, J=10.0 Hz, J=2.8 Hz, 1H, H_4), 5.67-5.98 (m, 2H, H_2, H_3), 6.15 (dd, J=10.0 Hz, J=2.8 Hz, 1H, H_5); IR (CCl_4): ν 1715 (C=O), 1650, 1595, 1250, 1240, 1070 cm^{-1}; EI/MS: m/e 204 (M^+), 189 (M-CH_3), 131 (M-COOEt), 91 (benzyl); Found 204.1152. $C_{13}H_{16}O_2$ requires 204.1150.

FVT of **1**

FVT of **1** (305 mg, 1.40 mmol) with sample temp.: 60-70 °C, oven temp.: 550 °C, cold trap temp.: -78 °C, p: 2.10^{-2} mm Hg produced a mixture of **38** and **41** (196 mg, molar ratio 1:1, ^{1}H-NMR, Cap.GC). Variation of the oven temp.(400-600 °C) did not affect the product ratio. Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3) gave **38** (97 mg, 36 %, Rf = 0.50) and **41** (55 mg, 13 %, Rf = 0.15). *Ethyl* cis-3*a*,7*a*-*dihydroindene* 6-*carboxylate* **38**: ^{1}H-NMR: δ 1.30 (t, J=7.1 Hz, 3H, OCH$_2$CH$_3$), 2.16-2.51 (m, 1H, H_1), 2.62-3.00 (m, 1H, H_1), 3.02-3.43 (m, 1H, H_{7a}), 3.43-3.61 (m, 1H, H_{3a}), 4.21 (q, J=7.1 Hz, 2H, OCH$_2$), 5.53-5.97 (m, 3H, H_2, H_3, H_4), 6.25 (dt, J=9.9 Hz, J=1.7 Hz, 1H, H_5), 6.83 (d, J=4.7 Hz, 1H, H_7); IR (CCl_4): ν 3050, 1715 (C=O), 1640, 1590, 1250, 1075 cm^{-1}; EI/MS: m/e 190 (M^+), 161, 145, 117 (M-COOEt), 91 (benzyl); Found 190.0998. $C_{12}H_{14}O_2$ requires 190.0994. *Diethyl* 5,10-*dioxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene* 2,8-*dicarboxylate* **41**: ^{1}H-NMR: δ 1.38 (t, J=7.0 Hz, 6H, 2xOCH$_2$CH$_3$), 3.38 (d, J=5.0 Hz, 1H, H_6), 3.69 (dd, J =3.9 Hz, ^{4}J=1.3 Hz, 1H, H_1), 3.99

(br d, J=5 0 Hz, 1H, H_7), 4 08-4 40 (m, 4H, 2xOCH_2CH_3), 6 37 (d, ^{3}J=5 7 Hz, 1H, H_4), 7 12 (dd, J=3 9 Hz, ^{4}J=1 3 Hz, 1H, H_9), 7 45 (d, J=5 7 Hz, 1H, H_3), IR (CCl_4) ν 1800 (C=O, bridged), 1720 (C=O), 1590 (C=C, unsat), 1265, 1225, 1100, 910 cm^{-1}, CapGC/CI/MS m/e 305 (M^++1), 277 (M+1-CO), 231 (M-COOEt), 203 (M-CO-COOEt), Found 305 1037 $C_{16}H_{17}O_6$ requires 305 1025 Analogously, by using 6-*D*-**1** instead of **1**, 7-*deuterio*-**38** and 6,7-*dideuterio*-**41** were prepared

Diethyl 2,7-*dimethyl*-1-*oxo*-cis-3*a*,7*a*-*dihydroindene* 3,6-*carboxylate* **36**

FVT of **35** (43 mg, 0 13 mmol) with sample temp 120 °C, oven temp 450 °C, cold trap temp -78 °C, p 4 10^{-2} mm Hg, gave **36** and **37** (33 mg, 1 1 molar mixture, 35 % yield each (^{1}H-NMR)) These compounds were not separated **36** ^{1}H-NMR δ 1 31 (t, J=7 0 Hz, 3H, C_6-$CO_2CH_2CH_3$), 1 40 (t, J=7 0 Hz, 3H, C_3-$CO_2CH_2CH_3$), 2 09 (d, J=1 8 Hz, 3H, C_2-CH_3), 2 40 (s, 3H, C_7-CH_3), 3 24 (d, J=9 4 Hz, 1H, H_{7a}), 4 00-4 53 (m, 5H, H_{3a}, 2xOCH_2CH_3), 5 78 (dd, J=10 Hz, J=2 8 Hz, 1H, H_4), 6 19 (dd, J=10 Hz, J=2 4 Hz, 1H, H_5)

Diethyl 1-*oxo*-cis-3*a*,7*a* *dihydroindene* 3*a*,6-*dicarboxylate* **42**

FVT of **41** (88 mg, 0 289 mmol), according to the procedure used for **36**, gave **42** and **43** (62 mg, 1 1 molar mixture, 32 % yield each (^{1}H-NMR)) ^{1}H-NMR δ 1 19-1 53 (m, 6H, 2xOCH_2CH_3), 4 09-4 58 (m, 5H, H_{7a}, 2xOCH_2CH_3), 5 97 (d, J=10 Hz, 1H, H_4), 6 38 (d, J=5 7 Hz, 1H, H_2), 6 50 (d, J=10 Hz, 1H, H_5), 6 95 (d, J=5 1 Hz, 1H, H_7), 7 67 (d, J=5 7 Hz, 1H, H_3)

Diethyl 3-*oxo*-*indane* 1,5-*dicarboxylate* **43**

Ester **41** (134 mg, 0 441 mmol) was heated in DMF as described for the preparation of **37**, to yield **43** (106 mg, 87 %) as a pure oil after flash chromatography (Al_2O_3, EtOAc /*n*-hexane = 1/10) ^{1}H-NMR δ 1 19-1 53 (m, 6H, 2xOCH_2CH_3), 2 91 A of ABX (dd, J=19 5 Hz, J=8 1 Hz, 1H, H_2), 3 27 B of ABX (dd, J=19 5 Hz, J=3 9 Hz, 1H, H_2), 4 09-4 58 (m, 5H, 2xOCH_2, H_1), 7 78 (d, J=8 1 Hz, 1H, H_7), 8 33 (dd, J=8 1 Hz, J=1 5 Hz, 1H, H_6), 8 43 (d, J=1 5 Hz, 1H, H_4), ^{13}C-NMR δ 14 0 (q, 2xOCH_2CH_3), 39 5 (t, C_2), 43 8 (d, C_1), 61 3 (t, OCH_2), 61 7 (t, OCH_2), 125 1 (d), 126 5 (d), 131 6 (s), 135 5 (d), 136 6 (s, C_{3a}, C_4, C_6, C_7, C_{7a}), 155 2 (s, C_5), 165 7 (s), 171 5 (s, C_1-CO, C_5-CO), 204 2 (s, C_3), IR (CCl_4) ν 2980, 1725 (C=O), 1610, 910 cm^{-1}, EI/MS m/e 276 (M^+), 231 (M-OEt), 203 (M COOEt), 175 (M CO COOEt), Found 276 0997 $C_{15}H_{16}O_5$ requires 276 0998

Ethyl exo-4-*methyl*-5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* endo-3-*carboxylate* **51a**

Excess Zn powder (995 mg, 15 2 mmol) was added to a soln of **34a** (405 mg, 1 746 mmol) in AcOH (10 ml) in a N_2 atmosphere and stirred for 1 5 h at 110 °C After cooling to r t the remaining Zn was removed by filtration AcOH was concentrated *in vacuo* to afford **51a** (342 mg, 84 %), that solidified after flash chromatography (EtOAc /*n*-hexane = 1/3, Rf = 0 30, I_2, purity by Cap GC > 99 %) M p 73-75 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 0 97 (d, J=6 4 Hz, 3H, C_4-Me), 1 36 (t, J=7 Hz, 3H, OCH_2CH_3), 1 49 (br s, 1H, H_{10}), 1 62 (br s, 1H, H_{10}), 2 47 (dq, $J_{3,4}$=11 7 Hz,

J=6.4 Hz, 1H, H_4), 2.60-3.36 (m, 5H, H_1, H_2, H_3, H_6, H_7), 4.26 and 4.28 (q,q, J=7 Hz, 2H, diastereotopic OCH_2CH_3), 5.96-6.20 (m, 2H, H_8, H_9); ^{13}C-NMR: δ 13.7 (q), 13.9 (q, C_3-$COOCH_2CH_3$, C_4-CH_3), 41.2 (d), 45.9 (d), 46.9 (d), 47.4 (d), 48.9 (d, C_1, C_2, C_4, C_6, C_7), 52.2 (t, C_{10}), 53.8 (d, C_3), 60.3 (t, C_3-$COOCH_2$), 134.7 (d), 135.9 (d, C_8, C_9), 173.0 (s, C_3-CO), 219.6 (s, C_5); IR (KBr): ν 2975, 1725 (C=O), 1365, 1230, 1220, 1185 cm^{-1}; EI/MS: m/e 234 (M^+), 169 ($M-C_5H_5^+$), 161 (M-COOEt), 66 (C_5H_6); MS: Found 234.1246. $C_{14}H_{18}O_3$ requires 234.1256. Found C, 70.93; H, 7.71. $C_{14}H_{18}O_3$ requires C, 71.77; H, 7.74.

Ethyl exo-4-*ethyl*-5-*oxo*-endo-*tricyclo*[5.2.1.0^{2,6}]*dec*-8-*ene* endo-3-*carboxylate* **51b**

The zinc reduction of **34b** was carried out as described for the synthesis of **51a** starting from Zn powder (550 mg, 8.41 mmol), **34b** (165 mg, 0.671 mmol) and AcOH (8 ml) to afford **51b** (143 mg, 85 %) as a pure oil after flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3, Rf = 0.3, I_2). ^{1}H-NMR: δ 0.82 (t, J=7 Hz, 3H, C_4-CH_2CH_3), 1.13-1.82 (m, 7H, OCH_2CH_3, H_{10}, C_4-CH_2), 2.26-2.54 (m, 1H, H_4), 2.78-3.34 (m, 5H, H_1, H_2, H_3, H_6, H_7), 4.05-4.42 (m, 2H, diastereotopic OCH_2CH_3), 5.96-6.20 (m, 2H, H_8, H_9); IR (CCl_4): ν 2960, 1732 (C=O, ester), 1220, 1170, 1157 cm^{-1}; EI/MS: m/e 248 (M^+), 220 (M-CO), 203 ($M-OEt^+$), 183 ($M-C_5H_5^+$), 66 (C_5H_6); Found 248.1418. $C_{15}H_{20}O_3$ requires 248.1412.

Ethyl exo-4-*allyl*-5-*oxo*-endo-*tricyclo*[5.2.1.0^{2,6}]*dec*-8-*ene* endo-3-*carboxylate* **51c**

Application of the same procedure as described for the preparation of **51a** using Zn (300 mg, 4.59 mmol), AcOH (5 ml) and **34c** (70 mg, 0.271 mmol) gave **51c** (70 mg, 90 %, purity by CapGC = 90 %) after flash chromatographic purification (silica gel, EtOAc /*n*-hexane = 1/3, Rf = 0.37, I_2). ^{1}H-NMR: δ 1.34 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.58 (s, 2H, H_{10}), 1.87-2.73 (m, 3H, H_4, C_4-CH_2), 2.80-3.31 (m, 5H, H_1, H_2, H_3, H_6, H_7), 4.11-4.38 (m, 2H, diastereotopic OCH_2CH_3), 4.85-5.11 (m, 2H, C_4-CH_2CHCH_2), 5.40-5.89 (m, 1H, C_4-CH_2CH), 5.98-6.23 (m, 2H, H_8, H_9); IR (CCl_4): ν 1735 (C=O, ester), 1635 (C=C), 1160 cm^{-1}; EI/MS: m/e 260 (M^+), 195 ($M-C_5H_6^+$), 187 (M-COOEt), 66 (C_5H_6); Found 260.1414. $C_{16}H_{20}O_3$ requires 260.1412.

Ethyl exo-4-n-*heptyl*-5-*oxo*-endo-*tricyclo*[5.2.1.0^{2,6}]*dec*-8-*ene* endo-3-*carboxylate* **51d**

The same procedure as employed for the preparation of **51a** using Zn (700 mg, 10.7 mmol), AcOH (10 ml) and **34d** (207 mg, 0.655 mmol) produced **51d** (174 mg, 83 %) as a pure oil after flash chromatography (silica gel, gradient: EtOAc /*n*-hexane = 1/10 to 1/3, Rf = 0.40, EtOAc /*n*-hexane = 1/3, I_2). ^{1}H-NMR: δ 0.71-1.67 (m, 20H, C_4-$(CH_2)_6CH_3$, OCH_2CH_3, H_{10}), 2.22-2.56 (m, 1H, H_4), 2.67-3.31 (m, 5H, H_1, H_2, H_3, H_6, H_7), 4.23 and 4.24 (q,q, J=7.0 Hz, 2H, diastereotopic OCH_2CH_3), 5.96-6.20 (m, 2H, H_8, H_9); IR (CCl_4): ν 2920, 1732 (C=O), 1157 cm^{-1}; EI/MS: m/e 318 (M^+), 253 ($M-C_5H_5^+$), 66 (C_5H_6); Found 318.2200. $C_{20}H_{30}O_3$ requires 318.2195.

Trans-4-*methyl*-5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* 3 *carboxylic acid* **52a**

Ester **51a** (205 mg, 0 876 mmol) was dissolved in EtOH (4 5 ml)/2 N NaOH (1 5 ml) and refluxed for 10 min[35] After cooling to r t , the mixture was poured into water (25 ml) and extracted with Et_2O (3 x 30 ml) The water layer was acidified to pH 1 using HCl (20 % aq) and again extracted three times with Et_2O (acid-base extraction) The combined ether extracts were washed (H_2O), dried ($MgSO_4$) and concentrated to afford **52a** (155 mg, 86 %) as a 1 1 diastereomeric mixture of *trans*-acids M p 140 190 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 1 00 (d, J=6 8 Hz, 3H, C_4-CH_3), 1 16-1 78 (m, 2H, H_{10}), 1 91-3 38 (m, 6H, H_1, H_2, H_3, H_4, H_6, H_7), 5 98-6 27 (m, 2H, H_8, H_9), 7 00 (br s, 1H, COOH); Homonuclear decoupling at δ 1 00 gave δ 2 42 (d, J=11 2 Hz) and δ 2 78 (d, J=12 Hz), IR (CCl_4) ν 3500-2450 (COOH), 1736 (C=O), 1705 (C=O), 1260 cm^{-1}, CapGC/EI/MS of diastereomer 1 and 2 m/e 206 (M^+), 191 (M CH_3), 141 (M-$C_5H_5^+$), 66 (C_5H_6), Found 206 0939 $C_{12}H_{14}O_3$ requires 206 0943

Trans-4-*ethyl*-5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* 3-*carboxylic acid* **52b**

The same procedure as employed for the synthesis of **52a** was applied to **51b** (140 mg, 0 565 mmol) using EtOH (2 ml)/2 N NaOH (2ml) **52b** (128 mg, 100 %) was obtained as a 1 1 mixture of *trans*-diasteromers (Cap GC, ^{1}H-NMR) ^{1}H-NMR δ 0 82 (t, J=7 Hz, 3H, C_4-CH_2CH_3), 1 11-1 78 (m, 4H, H_{10}, C_4-CH_2), 2 22-3 33 (m, 6H, H_1, H_2, H_3, H_4, H_6, H_7), 5 98-6 31 (m, 2H, H_8, H_9), 7 80 (br s, 1H, COOH), IR (CCl_4) ν 3500-2500 (COOH), 1735 (C=O), 1705 (C=O), 1235 cm^{-1}, CapGC/EI/MS of diastereomer 1 and 2 m/e 220 (M^+), 175 (M COOH), 155 (M-$C_5H_5^+$), 66 (C_5H_6), Found 220 1099 $C_{13}H_{16}O_3$ requires 220 1099

Trans-4-*allyl* 5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* 3-*carboxylic acid* **52c**

The same procedure as employed for the synthesis of **52a** using **51c** (75 mg, 0 288 mmol) and FtOH (1 5 ml)/NaOH (1 5 ml) gave **52c** (68 mg, 100 %) as a 1 1 mixture of *trans*-diastereomers ^{1}H-NMR δ 1 49 A of AB (d, J=9 Hz, 1H, H_{10}), 1 70 B of AB (d, J= 9 Hz, 1H, H_{10}), 2 11-2 69 (m, 3H, H_4, C_4-CH_2), 2 73-3 36 (m, 5H, H_1, H_2, H_3, H_6, H_7), 4 87-5 16 (m, 2H, C_4-CH_2CHCH_2), 5 44-5 89 (m, 1H, C_4-CH_2CH), 6 00-6 27 (m, 2H, H_8, H_9), 7 35 (br s, 1H, COOH), IR (CCl_4) ν 3500 2500 (COOH), 1735 (C=O), 1705 (C=O, acid), 920 cm^{-1}, CapGC/EI/MS of diastereomer 1 and 2 m/e 232 (M^+), 167 (M $C_5H_5^+$), 66 (C_5H_6), Found 232 1095 $C_{14}H_{16}O_3$ requires 232 1099

Trans-4-n-*heptyl*-5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* 3-*carboxylic acid* **52d**

The same procedure as employed for the preparation of **52a**, using **51d** (240 mg, 0 755 mmol) and EtOH (6 3 ml)/NaOH (6 3 ml), gave **52d** (202 mg, 92 %) as a 1 1 mixture of *trans*-diastereomers ^{1}H-NMR δ 0 73 1 78 (m, 17H, C_4-$(CH_2)_6CH_3$, H_{10}), 2 16-2 58 (m, 1H, H_4), 2 62-3 36 (m, 5H, H_1, H_2, H_3, H_6, H_7), 6 00-6 31 (m, 2H, H_8, H_9), 7 40 (br s, 1H, COOH), IR (CCl_4) ν 3500-2450 (COOH), 1735 (C=O), 1705 (C=O, acid) cm^{-1}, EI/MS m/e 290 (M^+), 272 (M-H_2O), 225 (M-$C_5H_5^+$), 66 (C_5H_6), Found 290 1874 $C_{18}H_{26}O_3$ requires 290 1882

Ethyl trans-5-*methyl*-4-*oxocyclopent*-2-*ene* 1-*carboxylate* **53a**

FVT of **51a** (50 mg, 0 214 mmol) (sample temp 70 °C, oven temp 510 °C, cold trap temp -78 °C, p 2 10 ^{2} mm Hg) yielded **53a** (33 mg, 92 %, 99 % purity by CapGC) as a pure oil after flash chromatography (silica gel, EtOAc /*n* hexane = 1/3, Rf = 0 2) ^{1}H-NMR δ 1 29 (d, J=7 2 Hz, 3H, C_5-CH_3), 1 30 (t, J=7 2 Hz, 3H, OCH_2CH_3), 2 68 (qd, J=7 2 Hz, J=3 2 Hz, 1H, H_5), 3 42 (q, J≅3 Hz, 1H, H_1), 4 22 (q, J=7 2 Hz, 2H, OCH_2), 6 23 (dd, $^{3}J_{cis}$=5 8 Hz, ^{4}J=2 2 Hz, 1H, H_3), 7 63 (dd, $^{3}J_{cis}$=5 8 Hz, ^{4}J=2 6 Hz, 1H, H_2), IR (CCl_4) ν 2970, 1735 (C=O, ester), 1720 (C=O, ketone), 1590 (C=C, unsat), 1320, 1180 cm $^{-1}$, EI/MS m/e 168 (M^+), 122 (M-HOEt), 95 (M-COOEt), 67, Found 168 0792 $C_9H_{12}O_3$ requires 168 0786

Ethyl trans-5-*ethyl*-4-*oxocyclopent*-2-*ene* 1-*carboxylate* **53b**

FVT of **51b** (30 mg, 0 121 mmol) (sample temp 70 °C, oven temp 510 °C, cold trap temp -78 °C, p 2 10 ^{2} mm Hg) gave **53b** (20 mg, 90 %) as a pure oil after flash chromatography (silica gel, EtOAc /*n* hexane = 1/3, Rf = 0 3, I_2) ^{1}H-NMR δ 0 98 (t, J=7 4 Hz, 3H, C_5-CH_2CH_3), 1 30 (t, J=7 1 Hz, 3H, OCH_2CH_3), 1 44-2 13 (m, 2H, C_5-CH_2), 2 56-2 78 (m, 1H, H_5), 3 52 (q, J≅2 4 Hz, 1H, H_1), 4 22 (q, J=7 1 Hz, 2H, OCH_2), 6 23 (dd, $^{3}J_{cis}$=5 8 Hz, ^{4}J= 2 2 Hz, 1H, H_3), 7 63 (dd, $^{3}J_{cis}$=5 8 Hz, ^{4}J=2 6 Hz, 1H, H_2), IR (CCl_4) ν 2960, 1740 (C=O, ester), 1710 (C=O, ketone), 1590 (C=C, unsat) cm $^{-1}$, EI/MS m/e 182 (M^+), 154 (M-CO), 109 (M-COOEt), 81 ($C_5H_5O^+$), Found 182 0934 $C_{10}H_{14}O_3$ requires 182 0943

Ethyl trans-5-*allyl*-4-*oxocyclopent*-2-*ene* 1-*carboxylate* **53c**

FVT of **51c** (30 mg, 0 115 mmol) (sample temp 95 °C, oven temp 510 °C, cold trap temp -78 °C, p 2 10 ^{2} mm Hg) gave **53c** (19 mg, 85 %, 98 % purity by CapGC) as a pure oil after flash chromatography (silica gel, EtOAc /*n* hexane = 1/3, Rf = 0 20) ^{1}H-NMR δ 1 30 (t, J=7 2 Hz, 3H, OCH_2CH_3), 2 16-2 71 (m, 2H, C_5-CH_2), 2 71-2 93 (m, 1H, H_5), 3 56 (q, J≅2 6 Hz, 1H, H_1), 4 21 (q, J=7 2 Hz, 2H, OCH_2), 4 96-5 25 (m, 2H, C_5-CH_2CHCH_2), 5 49-5 96 (m, 1H, C_5-CH_2CH), 6 22 (dd, ^{3}J=5 8 Hz, ^{4}J=2 4 Hz, 1H, H_3), 7 62 (dd, ^{3}J=5 8 Hz, ^{4}J=2 6 Hz, 1H, H_2), IR (CCl_4) ν 2975, 2920, 1740 (C=O, ester), 1715 (C=O, ketone), 1637 (C=C), 1587 (C=C, unsat), 1325, 1030 cm $^{-1}$, EI/MS m/e 194 (M^+), 166 (M CO), 148 (M HOEt), 121 (M COOEt), Found 194 0947 $C_{11}H_{14}O_3$ requires 194 0943

Ethyl trans-5-n-*heptyl*-4-*oxocyclopent*-2-*ene* 1-*carboxylate* **53d**

Ester **51d** (67 mg, 0 211 mmol) was subjected to FVT as described above for the preparation of **52a** (sample temp 130 °C) to give **53d** (50 mg, 94 %) as a pure oil ^{1}H-NMR δ 0 73-2 03 (m, 18H, C_5-C_7H_{15}, OCH_2CH_3), 2 56-2 78 (m, 1H, H_5), 3 49 (q, J≅2 5 Hz, 1H, H_1), 4 20 (q, J=7 1 Hz, 2H, OCH_2), 6 23 (dd, $^{3}J_{cis}$=5 6 Hz, ^{4}J= 2 4 Hz, 1H, H_3), 7 61 (dd, $^{3}J_{cis}$=5 6 Hz, ^{4}J=2 6 Hz, 1H, H_2), IR (CCl_4) ν 2920, 1740 (C=O, ester), 1720 (C=O, ketone), 1590 (C=C, unsat) cm $^{-1}$, EI/MS m/e 253 (M^++1), 179

(M-COOEt), 154 (M+1-C_7H_{15}), 108 (M+1-C_7H_{15}-HOEt), Found 252 1727 $C_{15}H_{24}O_3$ requires 252 1725

Ethyl trans-2-*methyl*-3-*oxocyclopentane* 1-*carboxylate* **54a**

53a (20 mg, 0 119 mmol) was hydrogenated in EtOH for 30 min at r t at normal pressure using Pd/C as catalyst, to furnish **54a** (18 mg, 89 %) as a pure oil ^{1}H-NMR δ 1 15 (d, J≅7 0 Hz, 3H, C_2-CH_3), 1 26 (t, J=7 2 Hz, 3H, OCH_2CH_3), 1 90-2 75 (m, 6H, H_1, H_2, H_4, H_5), 4 20 (q, J=7 2 Hz, 2H, OCH_2), IR (CCl_4) ν 2920, 1745 (C=O, ketone), 1730 (C=O, ester), 1145 cm^{-1}, EI/MS m/e 170 (M^+), 142 (M-CO), 97 (M-COOEt), Found 170 0937 $C_9H_{14}O_3$ requires 170 0943

Ethyl trans-2-*ethyl*-3-*oxocyclopentane* 1-*carboxylate* **54b**

Ester **53b** (15 mg, 0 0824 mmol) was hydrogenated as described for the preparation of **54a** to yield pure **54b** (12 mg, 79 %) as an oil after flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3, Rf = 0 3, I_2) ^{1}H NMR δ 0 91 (t, J=7 2 Hz, 3H, C_2-CH_2CH_3), 1 29 (t, J=7 1 Hz, 3H, OCH_2CH_3), 1 36-2 60 (m, 7H, H_2, H_4, H_5, C_2-CH_2), 2 62-3 00 (m, 1H, H_1), 4 20 (q, J=7 1 Hz, 2H, OCH_2), IR (CCl_4) ν 2960, 1745 (C=O, ketone), 1735 (C=O, ester), 1375, 1195, 1177, 1155 cm^{-1}, EI/MS m/e 184 (M^+), 156 (M-CO), 111 (M-COOEt), 83 ($C_5H_7O^+$), Found 184 1093 $C_{10}H_{16}O_3$ requires 184 1099

Ethyl trans-2-n-*heptyl*-3-*oxocyclopentane* 1-*carboxylate* **54d**

Ester **53d** (18 mg, 0 0714 mmol) was hydrogenated as described for **54a** to afford **54d** (18 mg, 99 %) as an oil ^{1}H-NMR δ 0 73-2 97 (m, 24H, C_2-C_7H_{15}, H_1, H_2, H_4, H_5, OCH_2CH_3), 4 20 (q, J=7 0 Hz, 2H, OCH_2), IR (CCl_4) ν 2920, 1745 (C=O, ketone), 1730 (C=O, ester), 1375 cm^{-1}, EI/MS m/e 254 (M^+), 226 (M-CO), 209 (M+1-HOEt), 181 (M-COOEt), 156 (M+1-C_7H_{15}), 83 ($C_5H_7O^+$), Found 254 1873 $C_{15}H_{26}O_3$ requires 254 1882

Trans-5-*methyl* 4-*oxocyclopent*-2-*ene* 1-*carboxylic acid* **50a**

52a (72 mg, 0 35 mmol) was subjected to FVT sample temp 110 °C, oven temp 510 °C, p 2 10^{-2} mm Hg, cold trap temp -78 °C to produce **50a**[35] (48 mg, 98 %) as a pale-yellow pure oil ^{1}H-NMR δ 1 28 (d, J=7 Hz, 3H, C_5-CH_3), 2 68 (qd, J=7 2 Hz, J=3 2 Hz, 1H, H_5), 3 44 (m, 1H, H_1), 6 25 (dd, $^3J_{cis}$=5 8 Hz, ^{4}J= 2 1 Hz, 1H, H_3), 7 63 (dd, $^3J_{cis}$=5 8 Hz, ^{4}J=2 5 Hz, 1H, H_2), 7 78 (br s, 1H, COOH), IR (CCl_4) ν 3500-2500 (COOH), 1710 (C=O), 1590 (C=C, unsat) cm^{-1}, EI/MS m/e 140 (M^+), Found 140 0471 $C_7H_8O_3$ requires 140 0473

Trans-5-*ethyl*-4-*oxocyclopent*-2-*ene* 1-*carboxylic acid* **50b**

Acid **52b** (97 mg, 0 441 mmol) was subjected to FVT (sample temp 110-115 °C, oven temp 510 °C, p 2 10^{-2} mm Hg, cold trap temp -78 °C) to furnish **50b** (58 mg, 85 %) as a pale-yellow pure oil ^{1}H-NMR δ 0 99 (t, J=7 3 Hz, 3H, C_5 CH_2CH_3), 1 29 2 13 (m, 2H, C_5-CH_2), 2 69 (qd, J=4 8 Hz, J=3 2 Hz, 1H, H_5), 3 59 (q, J≅2 6 Hz, 1H, H_1), 6 29 (dd, J=5 8 Hz, J=2 2 Hz, 1H, H_3), 7 66 (dd, J=5 8 Hz,

J=2 6 Hz, 1H, H_2), 7 71(br s, 1H, COOH), IR (CCl_4) ν 3500-2500 (COOH), 1710 (C=O) cm^{-1}, EI/MS m/e 154 (M^+), 126 (M-CO), 108 (M-COOH), 81 ($C_5H_5O^+$), Found 154 0635 $C_8H_{10}O_3$ requires 154 0630

Trans-5-*allyl*-4-*oxocyclopent*-2-*ene* 1-*carboxylic acid* **50c**

Acid **52c** (53 mg, 0 228 mmol) was subjected to FVT as described for **52a** to yield **50c** (35 mg, 92 %) as a pure oil ^{1}H-NMR δ 2 18-2 69 (m, 2H, C_5-CH_2), 2 73-2 98 (m, 1H, H_5), 3 63 (q, J≅2 5 Hz, 1H, H_1), 4 98-5 20 (m, 2H, C_5-CH_2CHCH_2), 5 47-5 96 (m, 1H, C_5-CH_2CH), 6 27 (dd, J=5 8 Hz, J=2 2 Hz, 1H, H_3), 7 30 (br s, 1H, COOH), 7 65 (dd, J=5 8 Hz, J=2 6 Hz, 1H, H_2), IR (CCl_4) ν 3500-2500 (COOH), 1715 (C=O), 1590 (C=C, unsat) cm^{-1}, EI/MS. m/e 166 (M^+), 149 (M-OH), Found 166 0628 $C_9H_{10}O_3$ requires 166 0630

Trans-5-n-*heptyl*-4-*oxocyclopent*-2-*ene* 1-*carboxylic acid* **50d**

Acid **52d** (197 mg, 0 679 mmol) was subjected to FVT as described for **52a** to yield **50d** (138 mg, 91 %) as a pure oil ^{1}H-NMR δ 0 73-2 89 (m, 16H, C_5-C_7H_{15}, H_2), 3 56 (q, J≅2 5 Hz, 1H, H_1), 6 27 (dd, J=5 6 Hz, J=2 6 Hz, 1H, H_3), 7 64 (dd, J=5 6 Hz, J=2 4 Hz, 1H, H_2), 7 30 (br s, 1H, COOH), IR (CCl_4) ν 3500-2500 (COOH), 1710 (C=O) cm^{-1}, CI/MS m/e 225 (M^++1), 181 (M+1 CO_2), Found 225 1483 $C_{13}H_{21}O_3$ requires 225 1491

Trans-2-*methyl*-3-*oxocyclopentane* 1-*carboxylic acid* **45a**

Acid **50a** (41 mg, 0 293 mmol) was hydrogenated in EtOH for 30 min at r t at normal pressure using Pd/C as catalyst, to furnish **45a** (35 mg, 84 %) as a viscous oil after acid-base extraction **45a** slowly solidified by stirring in *n*-hexane M p 83-88 °C (lit[34] 94-95 °C, lit[38] 91-92 5 °C) ^{1}H-NMR δ 1 16 (d, J≅7 Hz, 3H, C_2-CH_3), 1 90-2 90 (m, 6H, H_1, H_2, H_4, H_5), 8 10 (br s, 1H, COOH), IR (KBr) ν 3400-2600 (COOH), 1740 (C=O) cm^{-1}, EI/MS m/e 142 (M^+), 97 (M-COOH), Found 142 0635 $C_7H_{10}O_3$ requires 142 0630

Trans-2-*ethyl*-3-*oxocyclopentane* 1-*carboxylic acid* **45b**

Acid **50b** (56 mg, 0 364 mmol) was hydrogenated as described for **45a** to afford **45b** (51 mg, 90 %) which slowly solidified after acid-base extraction (Et_2O) M p 37 42 °C (after recrystallization from *n*-hexane)(lit[33] 42 45 °C) ^{1}H-NMR δ 0 96 (t, J=7 2 Hz, 3H, C_2-CH_2CH_3), 1 33-2 62 (m, 7H, H_2, H_4, H_5, C_2 CH_2), 2 69-3 07 (m, 1H, H_1), 9 05 (br s, 1H, COOH), IR (CCl_4) ν 3500 2500 (COOH), 1745 (C=O, ketone), 1705 (C=O, acid) cm^{-1}, EI/MS m/e 156 (M^+), 128 (M-CO), 111 (M COOH), 83 ($C_5H_7O^+$), Found 156 0795 $C_8H_{12}O_3$ requires 156 0786

Trans 2 n *heptyl*-3-*oxocyclopentane* 1-*carboxylic acid* **45d**

Acid **50d** (138 mg, 0 616 mmol) was hydrogenated as described for **45a** to produce **45d** (107 mg, 77 %) which solidified after acid base extraction (Et_2O) M p 57 59 5 °C (after recrystallization from

n-hexane). ^{1}H-NMR: δ 0.73-2.66 (m, 20H, C_2-C_7H_{15}, H_2, H_4, H_5), 2.66-3.02 (m, 1H, H_1), 9.96 (br s, 1H, COOH); ^{13}C-NMR: δ 13.8 (CH_3), 22.4 (CH_2CH_3), 24.6 ($CH_2CH_2CH_3$), 26.5 ($CH_2C_3H_7$), 28.8 ($(CH_2)_2C_4H_9$), 29.4 (C_2-CH_2), 31.6 (C_5), 37.1 (C_4), 46.4 (C_2), 51.9 (C_1), 180.4 (COOH), 217.5 (C_3); IR (KBr): ν 3300-2500 (COOH), 2915, 1732 (C=O, ketone), 1707 (C=O, acid), 1190 cm^{-1}; CI/MS: m/e 227 (M^++1), 181 (M-COOH), 128 (M+1-$C_7H_{15}^+$); Found 227.1645. $C_{13}H_{23}O_3$ requires 227.1647. Found C, 69.01; H, 9.81. $C_{13}H_{22}O_3$ requires C, 68.99; H, 9.80.

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APPENDIX

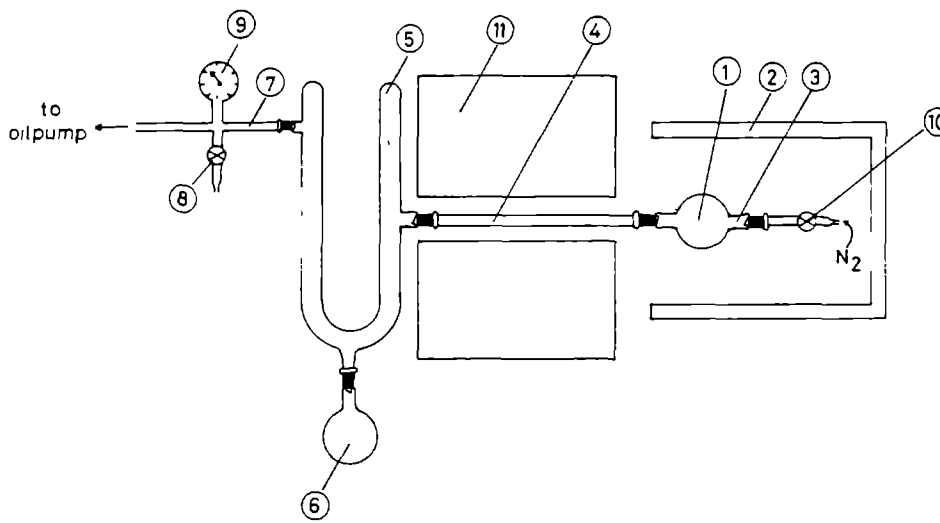
FLASH VACUUM THERMOLYSIS

A. Apparatus

The Flash Vacuum Thermolysis (FVT) apparatus, as developed at the Organic Laboratory of the Nijmegen University, is schematically depicted in Fig. 1.

Pyrex bulb (1) contains the substrate. This bulb is heated by means of a sublimation oven (2) (Büchi TO 50), which is shoved over it. The temperature of bulb (1) is measured by a thermocouple with a Digitron 2751-K thermometer. A gas inlet tube (3) (in cases when a carrier gas is required) or a stopple is attached to the socket of bulb (1). At the other end, bulb (1) is connected by means of Rotulex 19/9 cups and balls with the quartz oven tube (4) (inside diameter 16 mm; length 18 cm) in which the actual thermolysis process takes place. This oven tube is connected with the cold finger (5) by means of Rotulex 13/5 cups and balls. At the bottom of cold finger (5) a small round-bottomed

Fig. 1



flask (6) (in which the product is collected) is coupled. At its left end, cold finger (5) is directly connected by means of Rotulex 29/19 cups and balls with part (7) which contains the de-aeration tab (8)

(through which dry air or N_2 can be added) and the pressure reading gauge (9) (Edwards PR-10K). At its other end, (7) is connected with the double cold trap system which protects the vacuum pump (Edwards, E2M8).

The carrier gas flow and the pressure in the system is controlled by a needle valve (10) (Hoke millimite). The oven tube is heated by a Heraeus BR 1.6/18 oven (11) and the temperature is controlled by a Heraeus RK 42 control unit.

B. Experimental Procedure

Both cold traps are cooled and the vacuum pump is started. After introduction of the sample into bulb (1), this is connected with the oven tube. Cold finger (5) is connected, the sublimation oven is shoved over bulb (1) and the entire apparatus is evacuated. The pressure is checked to remain constant (*ca.* 2.10^{-2} torr). The cold finger is cooled with liquid N_2 or CO_2/isopropanol. The oven is set to the required temperature and switched on. Finally, the sublimation oven is heated in order to effect a slow evaporation or sublimation of the substrate. After completion of the reaction the sublimation oven, oven and vacuum pump are switched off and then the system is allowed to attain atmospheric pressure by opening tab (8). The cold finger is disconnected and immediately locked with stopples. The cold finger is allowed to attain room temperature, the product dissolved and the solvent evaporated *in vacuo*.

Optimum conditions for each compound can be found by varying the following parameters: oven and preheating temperature as well as the flow rate of the carrier gas. In cases of a very slow sublimation or evaporation, glass beads can be added to the substrate in order to accelerate the reaction.

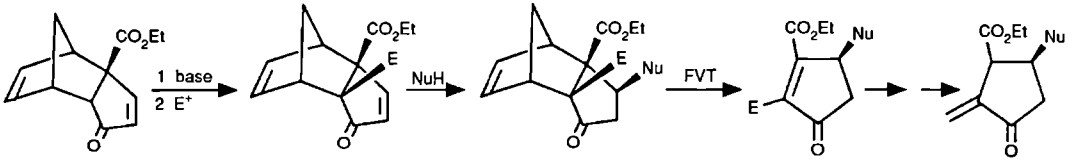
CHAPTER 3

SYNTHESIS OF BRIDGED NORBORNENE[4.3.3]OXAPROPELLANES AND THEIR BEHAVIOR IN NUCLEOPHILIC ADDITION REACTIONS

3.1 INTRODUCTION

The synthetic merits of tricyclo[5.2.1.$0^{2,6}$]decadienones for the preparation of a variety of functionalized cyclopentenones having an endo-cyclic double bond were described[1,2] in Chapter 1. The general Scheme 1 outlines the basis for the extension of the scope of this chemistry to exo-cyclic cyclopentenoids. The most attractive starting material is the Herz' ester **1**, that can readily be obtained from *p*-benzoquinone and cyclopentadiene[3]. In the preceding Chapter 2 the angular alkylation of **1** was extensively investigated[4,5].

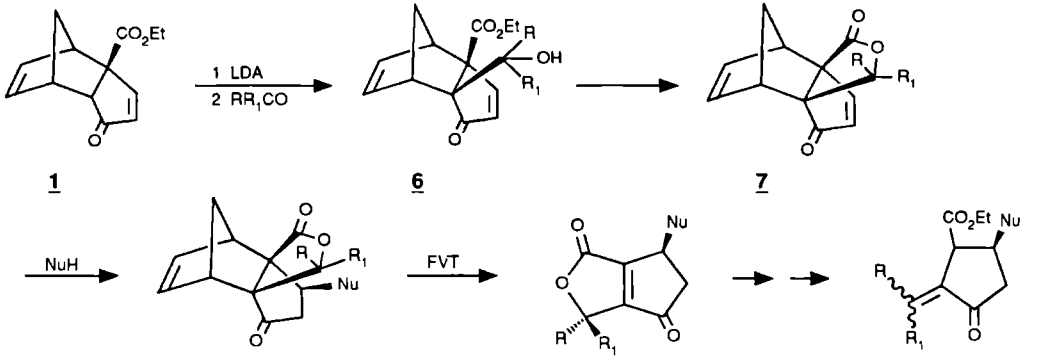
Scheme 1



1 **2** **3** **4** **5**

This Chapter will deal with the angular condensation, thus employing carbonyl compounds as electrophiles. Such condensations with ester **1** predictably will produce intermediate carbinols **6** which may undergo an intramolecular transesterification to give tetracyclic lactones **7** (Scheme 2).

Scheme 2



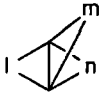
1 **6** **7**

8 **9** **10**

Subsequent conjugate addition followed by flash vacuum thermolysis is expected to produce annelated cyclopentenoid butenolides **9**, a hitherto unknown class of compounds. Finally, attempts

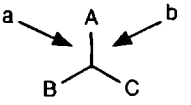
will be made to convert compounds **9** into sarkomycins **10** which have the exo-cyclic double bond. It will be shown that the preparation of the tetracyclic lactones **7** indeed can be realized. These lactones belong to the class of [4.3.3]propellanes, therefore some characteristics about these types of compounds will be briefly reviewed below.

Propellanes have been studied extensively in recent years for several reasons[6]. Small-ring propellanes **11** provided insight into the stability of highly strained systems as well as to the limits of carbon hybridization[7]. Various rearrangement reactions of propellane derivatives have been subject of study by organic chemists[8]. Since the three constituent rings of propellanes divide space into three distinct sectors, propellanes are well-suited to study the course of stereospecific and regiospecific reactions[9,10]. A Newman projection **12** along the central C-C-axis of a propellane is helpful in understanding the preference for reactions following either pathway a or b in terms of steric and/or stereoelectronic factors of the most adjacent ring.



l,m,n ≤ 2

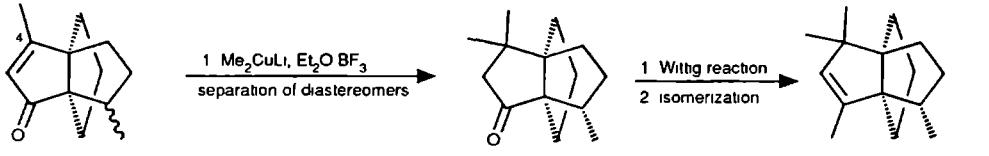
11



12

The occurrence of many naturally propellanes[6], *e.g.* the sesquiterpene modhephene **15**[11,12], has stimulated the interest in the control of the stereochemistry in these carbocyclic systems.

Scheme 3



13 **14** (30 %) **15** (87 %)

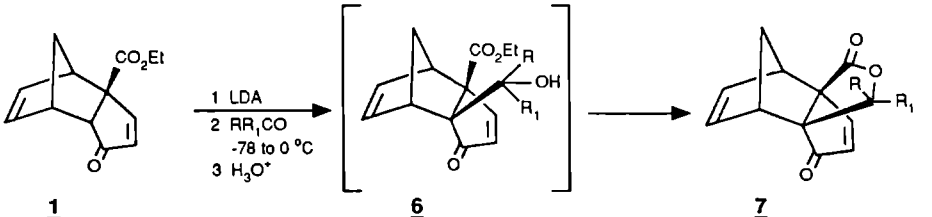
In their synthetic route to modhephene **15** (Scheme 3) Smith and Jerris[12] encountered a diminished tendency of the enone part of **13** to undergo conjugate addition with dimethylcopperlithium which was attributed to the effect of the neopentyl bridge adjacent to C_4. Also the reactivity of the carbonyl function in **14** is diminished by the presence of the adjacent propellane wing.

3.2 SYNTHESIS OF BRIDGED [4.3.3]OXAPROPELLANES BY ANGULAR CONDENSATION

Angular deprotonation of ester **1** with LDA and subsequent treatment with formaldehyde led to the

formation of 7a in yields ranging from 20 to 54 % (Scheme 4). This fluctuation in yield is due to excessive polymerization of the reactive formaldehyde when the condensation is scaled up to gram quantities. In this reaction gaseous formaldehyde was obtained by cracking paraformaldehyde[13] at temperatures up to 150 °C and then passing the monomeric aldehyde through a solution of angularly deprotonated 1 in THF. After work-up a mixture of carbinol 6a and lactone 7a was isolated. Cyclization of intermediate 6a to 7a was accomplished by stirring in dichloromethane with some *p*-toluenesulfonic acid at room temperature[14].

Scheme 4



1 6 7

	R	R_1	diastereomeric ratio	yield (%)		R	R_1	diastereomeric ratio	yield (%)
a	H	H	-	20-54	f	Et	H	syn/anti 1:1	82
b	H	Ph	anti > 95 %	69	g	n-Pr	H	syn/anti 1:1	80
c	t-Bu	H	syn > 95 %	50	h	i-Pr	H	syn/anti 1.9:1	73
d	n-hexyl	H	syn > 95 %	38	i	Me	Me	-	72
e	Me	H	syn/anti 1:1	71	j	$-(CH_2)_5-$		-	60

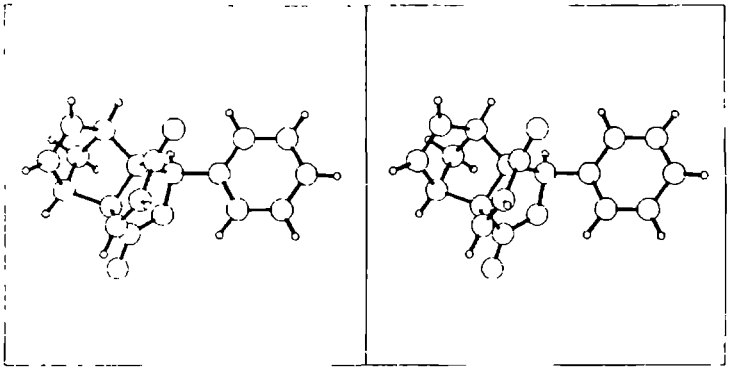
When deprotonated 1 was reacted with a series of aldehydes, the lactones 7 were isolated after work-up. In these cases the carbinols 6 were not isolated. It is well known that intramolecular reactions of functions that are covalently bonded in the same molecule, proceed at much faster rates than those involving intermolecular processes. This can be explained by differences in entropy and strain energy[15]. Apparently, lactonization of the intermediate carbinols 6 is a favorable process in which the Van der Waals interaction between the eclipsed 2-carboethoxy moiety and 6-hydroxyalkyl group is relieved. Force Field calculations using Allinger's program[16] indeed revealed a strong reduction of steric energy[17] in 7 in comparison with alcohols 6.

The formation of the bridged [4.3.3]oxapropellanes 7 from 1 appeared to be a highly stereoselective process in those cases in which rather bulky aldehydes were employed, such as benzaldehyde or pivalaldehyde. Condensation of 1 with *n*-heptanal also afforded only one diastereomer 7d, albeit in a yield of 36 %. This low yield is due to competitive self-condensation of *n*-heptanal. The analogous reaction with isobutyraldehyde led predominantly to one diastereomer in a diastereomeric excess of 30

%. When less bulky aldehydes were used the formation of equimolar diastereomeric mixtures was observed, *e.g.* with acetaldehyde. In the angular condensation of **1** with relatively bulky aldehydes there is apparently a considerable steric induction leading to the predominant formation of one diastereomer after lactonization.

In order to secure the correct stereochemistry at C_9 in bridged [4.3.3]oxapropellanes **7**, a single crystal X-ray diffraction analysis[18] of 9-phenyl-lactone **7b** was performed. The result of this structure analysis, which is shown in Fig. 1, reveals that the C_9-phenyl substituent in propellane **7b** has an *anti*-orientation with respect to its norbornene moiety.

Fig. 1



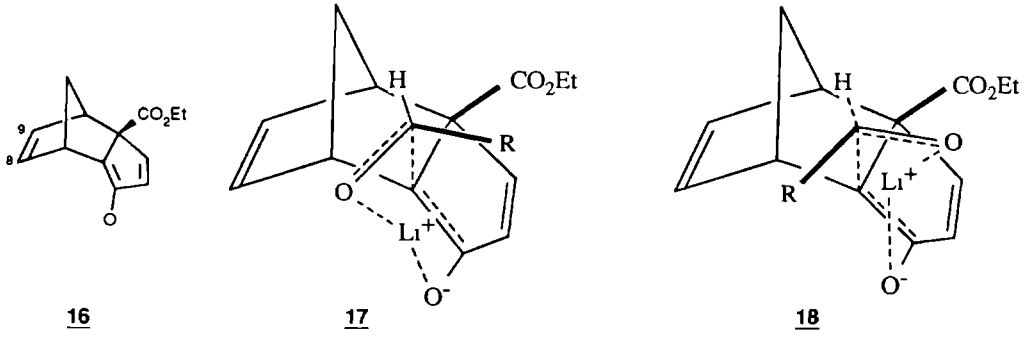
The spatial position of the substituent at C_9 is indicated by *syn* and *anti*. The norbornene moiety is taken as wing of reference. Hence, *anti* means that the substituent points away from the C_2-C_5 methylene bridge and *syn* means that the substituent points toward this bridge. Most unexpectedly, the stereoselective addition of the aliphatic aldehydes pivalaldehyde and *n*-heptanal to the enolate of **1**, to give **7c** and **7d**, respectively, appeared to proceed with completely opposite stereochemistry. Now the C_9 substituent has a *syn*-orientation. This conclusion was drawn from a scrutiny of the ^{1}H-NMR spectra of the C_9-alkyl substituted lactones **7c**,**d**,**h** and the phenyl lactone **7b**. In the ^{1}H-NMR spectra of **7c**,**d**,**h**, H_2 and H_5 appeared as separate broad singlets, the corresponding protons in **7b** and the epimer of **7h** overlap. This similarity in the ^{1}H-NMR spectra of **7b** and minor diastereomer **7h** points to the same stereochemistry around their C_9 centers. Moreover, H_9 of major diastereomer **7h** appears as a doublet (^{3}J=4.9 Hz) at δ 4.16 ppm which corresponds nicely with the δ-value of H_9 (δ 4.16 ppm) in *t*-butyl lactone **7c** . However, H_9 of the minor epimer of **7h** appears as a doublet (^{3}J=10.9 Hz) at δ 4.00 ppm. Unambiguous confirmation of these assignments of the stereochemistry at C_9 in **7c**,**d**,**h** was obtained at a later stage of this investigation from an X-ray diffraction study of an adduct derived from *t*-butyl substituted lactone **7c** (*vide infra*).

Mechanistically, the stereochemical preference for the formation of *syn*-9-alkyl substituted lactones

7 in the condensation of **1** with bulky aliphatic aldehydes can be satisfactorily explained by invoking chelation of the lithium cation with both the enolate **16** (Scheme 5) and the incoming carbonyl group in a six-membered chairlike transition state **17**[19] In such a pericyclic transition state, the bulky alkyl group will point away from the sterically demanding methylene bridge After C-C bond formation, rotation of 180° around this newly formed bond followed by lactonization will afford the observed diastereomer of the product It should be noted, that due to severe steric hindrance caused by the C_8-C_9 ethylene bridge in **16**, the addition of the aldehyde from the *endo*-face of the tricyclodecadienone system is very unlikely[1]

The factors governing the stereochemical course of the condensation of **16** with benzaldehyde are not fully understood yet In this case transition state **17** is apparently not the most favorable one, possibly because of a strong repulsion between the electron rich enolate system and the overlying phenyl group Hence, an alternative transition state should be invoked, which eventually leads to the observed stereochemistry Assuming again that the most bulky group is directed away from the methylene bridge in **16**, a plausible transition state would be **18** In such a transition state, metal chelation is also possible, however now in a six-membered boat conformation Although a boat-like transition state **18** seems less favorable than **17**, its occurrence should not be discounted because stabilization can now be gained by HOMO/LUMO interaction between the carbonyl function of the aldehyde and the electron-rich dienic system of **16** A similar explanation has been given by Mulzer *et al*[20] for the deviating stereochemical results in the addition of metalated carboxylic acids to aldehydes The preference of benzaldehyde as the only aldehyde for such a boat-like transition state **18** must be typically associated with the electronic features of the phenyl group

Scheme 5



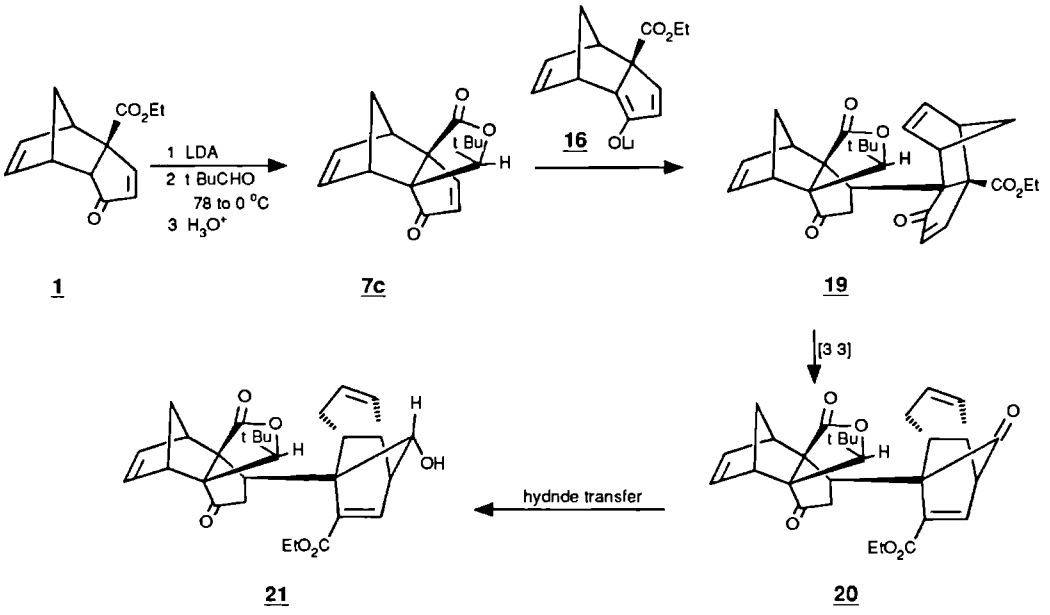
16 **17** **18**

The condensation of **1** with bulky aliphatic aldehydes or ketones appeared to be a rather slow process Evidently, this is the consequence of considerable steric interaction of the lithium enolate moiety and the vicinal carboethoxy group, as depicted in **17**, which destabilizes such a transition state Before lactonization can occur, subsequent rotation of 180° around the newly formed C-C bond is required Retro-aldol reaction may become an effective competing side reaction The observed high rate of the

benzaldehyde condensation with **1** confirms the occurrence of a different transition state as compared with the bulky aliphatic aldehydes

When the aldol reaction of **1** with pivalaldehyde was carried out on larger scale (9 mmol instead of 2 mmol) lactone **7** could not be isolated Instead, a dimeric adduct was obtained in *ca* 35 % yield, to which structure **21** was assigned on the basis of a single crystal X ray diffraction analysis[21] This deviant outcome may be the result of an increase of the concentrations of the reactants used The route leading to **21** is depicted in Scheme 6 Condensation of pivalaldehyde with **16** gives rise to the forma-

Scheme 6



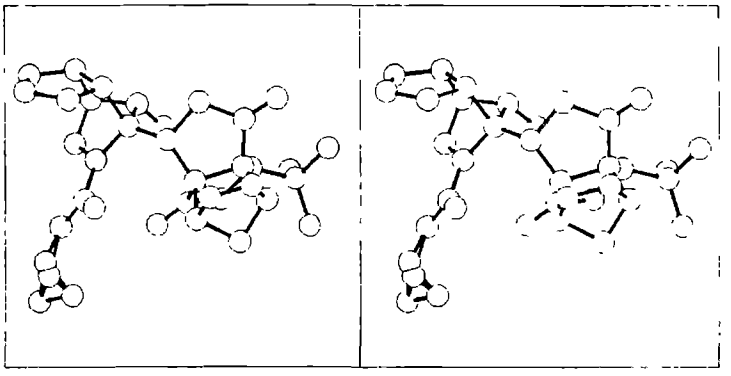
1 **7c** **19** **21** **20**

tion of lactone **7c** whose enone moiety in a subsequent step is stereoselectively attacked by enolate **16** to give **19** It should be mentioned that in this case no anion exchange between **16** and non-enolizable pivalaldehyde can occur (*Cf* cyclohexanone (Scheme 7)) The final steps in this route to **21** involve a Cope rearrangement of **19** into **20** (*Cf* Section 2 3 1), followed by a reduction of the strained bridge carbonyl group in **20**, ultimately furnishing alcohol **21** It remains speculative which reagent actually serves as the hydride donor in the conversion of **20** into **21** because there is no normal hydride donating agent present in the reaction mixture As will be shown in Chapter 6, LDA can act as a hydride donating species in reactions with non-enolizable tricyclodecenones and it is therefore suggested that LDA plays the role of hydride donor in this case as well However, the exact nature of this hydride addition remains uncertain because it takes place with a stereochemistry opposite to that described in Section 2 3 2 for an analogous hydride reduction employing $NaBH_4$ In principle, the reduction step can also take place before the Cope rearrangement This would involve a 1,2-attack from the shielded

concave-side in **19**, which is not very likely, but nevertheless cannot be rejected.

It should be noted that the X-ray structure determination of **21** also revealed the configuration at C_9 of the initially formed *t*-butyl lactone **7c** (Fig. 2), showing an inverted configuration in comparison

Fig. 2

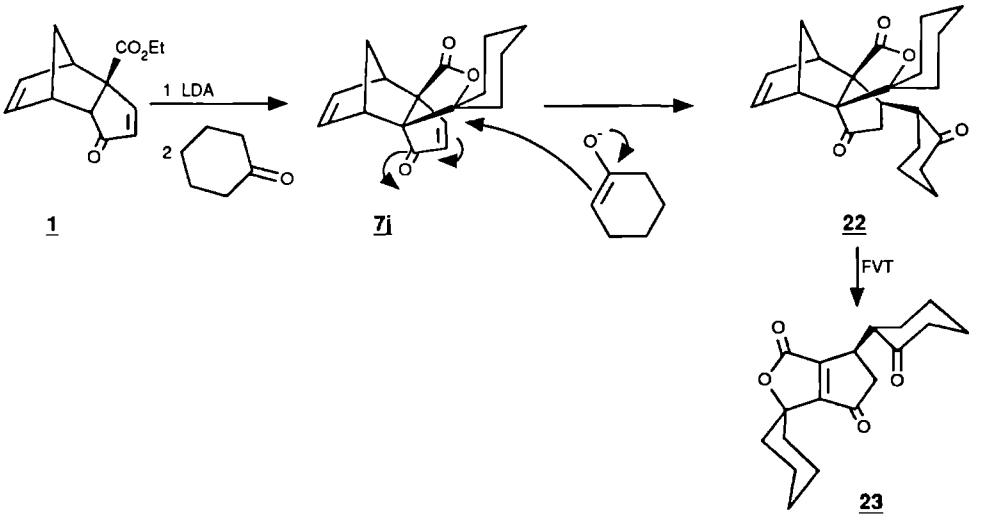


with 9-phenyl lactone **7b**. This X-ray determination therefore confirms the structural assignment that was based on the ^{1}H-NMR analyses of lactones **7c**,**d**,**h** (*vide supra*).

The condensation of **1** with ketones gave satisfactory results. For example, reaction of **1** with acetone smoothly afforded tetracyclic lactone **7i** in 72 % yield as a crystalline compound (Scheme 4). The analogous reaction of **1** with cyclohexanone produced the interesting spiropropellanolide[22] **7j** in a yield of 50 % (Scheme 7). However, attempts to scale up this reaction failed. Instead, **22** was obtained as the main product in a yield of 50 %, together with recovered **1** (20 %). The explanation for the formation of **22** involves an anion exchange between lithium enolate **16** and cyclohexanone. The resulting enolate of cyclohexanone then adds to the enone moiety of **7j** to yield **22**. A similar anion exchange was encountered in the reaction of **16** with benzyl bromide (Section 2.2). Apparently, the condensation-lactonization process yielding spirolactone **7j**, is not fast enough to prevent anion exchange or retro-aldol condensation to occur. The structure of **22** was ensured by performing FVT (520 °C) affording cyclopentenone derivative **23** in a high yield as an analytically pure crystalline compound.

This formation of **23** indicates that the tetracyclic lactones **7** are, unlike the 6-alkyl derivatives of **1** (Section 2.3.2), quite willing to undergo a stereoselective conjugate nucleophilic attack. It is noteworthy that in the reaction of **16** with cyclohexanone no addition product of the enolate of cyclohexanone with ester **1** was isolated. As both starting ester **1** and lactone **7j** are present in this reaction, the exclusive conjugate addition of the lithium enolate of cyclohexanone to the enone moiety of **7j** points to a higher reactivity of this enone moiety in comparison with that in ester **1**. Whereas Smith and Jerris[12] encountered a low tendency of [3.3.3]propellane **13** to undergo conjugate addition to its enone (Section 3.1) the enone moiety of bridged [4.3.3]oxapropellanolide **7j** is quite reactive in this respect. As can be deduced from molecular models of bridged [4.3.3]oxapropellanes **7**, conjugate nucleophilic

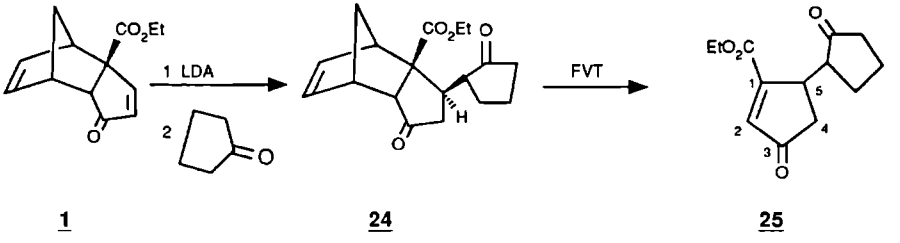
Scheme 7



attack of the enone moiety is not hampered by steric interaction between the incoming nucleophilic species and the lactone ring. This remarkable tendency of the enone part in tetracyclic lactones **7** to undergo conjugate additions will also be seen in other reagents (Section 3.3).

Reaction of tricyclic ester **1** with cyclopentanone did not produce lactone **7** but instead a mixture predominantly containing self-condensation products of cyclopentanone, some starting ester **1** and a minor amount of **24** was obtained (Scheme 8). Clearly, **24** has been formed by 1,4-addition of cyclopentanone enolate to **1**. Spiropentane derivatives in general possess an additional strain energy of

Scheme 8



about 8 kcal/mole due to the unfavorable sp^3-hybridization of the central quaternary carbon atom[22]. Probably this effect is thwarting the formation of the spiropentane analogue of **7j**. It is well known that cyclopentanone has a strong tendency to polymerize by selfcondensation reactions and therefore is diminishing its synthetic utility in aldol reactions[23]. Subjecting **24** to FVT gave cyclopentenone

derivative **25** in a high yield. In the ^{1}H-NMR spectrum of **25** its H_2-absorption appears as one characteristic doublet ($^4J_{H\,2,5}$= 2.2 Hz) at δ 6.75 ppm.

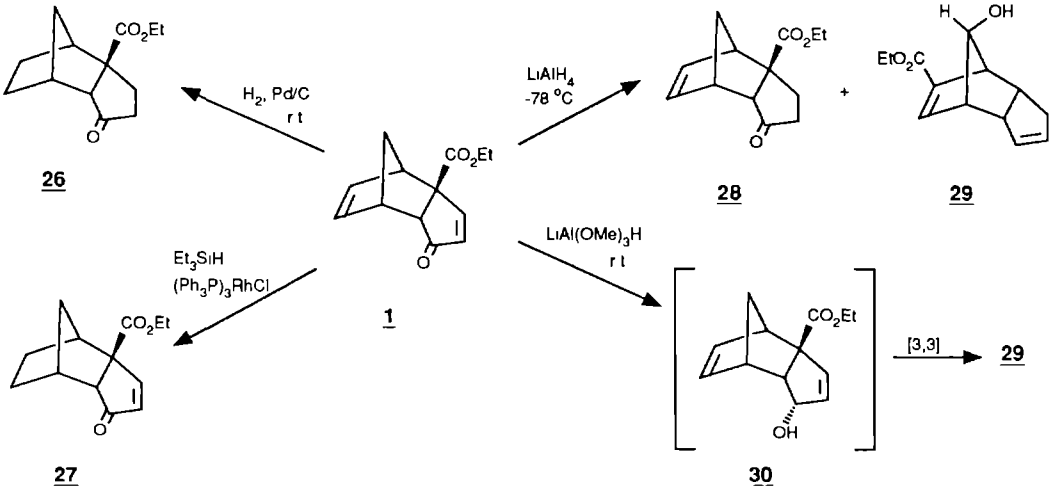
In conclusion, the aldol reactions of **1** with a variety of aldehydes and ketones give rise to the formation of bridged [4.3.3]oxapropellanes **7** in moderate to high yields. Lactonization of the intermediate carbinols **6** occurs smoothly but appeared to slow down when sterically demanding aliphatic aldehydes and ketones were employed. In those cases side reactions such as proton exchange and retro-aldol reactions become competitive. When bulky aldehydes are used the condensation/lactonization sequence proceeds with a high degree of stereoselectivity, the stereochemical outcome of which is strongly depending on the nature of the aldehydes. Aliphatic aldehydes show the opposite stereochemistry as compared with benzaldehyde. In the latter case stereoelectronic interaction between the phenyl group and the dienolate in **16** may play a crucial role in determining the ultimate structure of the condensation product.

3.3 REDUCTION OF BRIDGED [4.3.3]OXAPROPELLANES

In order to compare the enone reactivity of **1** and **7** the hydride addition to the enone moiety of ester **1** was investigated. Reductive processes of tricyclodecadienones, such as catalytic hydrogenation and reactions with various hydride donating reagents, sofar[24] have not been studied in detail. The major concern will be the chemoselective reduction of the enone part of **1** (1,2- *vs.* 1,4-selectivity) with leaving the reactive strained $C_{8\text{-}9}$ olefinic bond unaffected.

Catalytic hydrogenation (Pd/C) rapidly reduces both olefinic bonds without any selectivity to give **26** in high yield (Scheme 9). It is known[25] that treatment of α,β-enones with excess Et_3SiH in THF in

Scheme 9

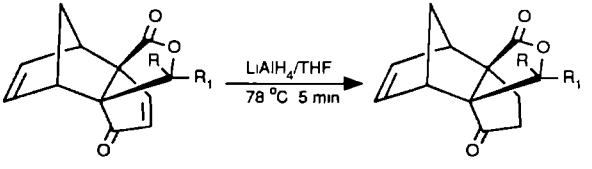


the presence of Wilkinson catalyst ($(PPh)_3Rh(I)Cl$) allows selective conjugate reduction of enones in the presence of isolated double bonds Surprisingly, prolonged reflux of **1** with this hydride donating reagent resulted in the selective reduction of the $C_{8,9}$ double bond furnishing **27**, together with some unreacted **1**, in 50 % yield (reaction conditions were not optimized) (Scheme 9) The deviating reactivity of the $C_{8,9}$ and $C_{3,4}$ double bond in this reaction may be an indication of an electronic interaction (either through bond or through space[26]) between these proximate olefinic bonds (the distance between the $C_{8,9}$ and $C_{3,4}$ olefinic bonds in **1** amounts to 2 7-2 8 Å)

Low temperatures usually favor kinetic 1,4- over 1,2-addition of organolithiums to α enones[27] Therefore, $LiAlH_4$ was used at low temperatures in order to accomplish a selective conjugate reduction of ester **1** After brief treatment of **1** with an excess of $LiAlH_4$ at -78 °C in THF the desired product **28**[28] was indeed formed in a yield of 51 % (Scheme 9), together with carbinol **29** as a by-product in a yield of 20 % Carbinol **29** was independently prepared in a yield of 79 % by employing the deactivated agent ('hard' according to the HSAB-principle[29]) $LiAlH(OMe)_3$ This reaction initially resulted in the stereoselective formation of the intermediate *endo*-alcohol **30** by 1,2-reduction, that then rearranged *via* a Cope rearrangement into *endo*-alcohol **29** (*Cf* Chapter 2) In the $LiAlH_4$ reduction of **1** mentioned above, both 1,2- and 1,4-hydride addition to the enone moiety is observed, giving **28** and **29** as the products

Reduction of bridged [4 3 3]oxapropellanes **7** with excess $LiAlH_4$ at -78 °C rapidly afforded the conjugatively reduced tetracyclic lactones **31** as sole products in almost quantitative yields (Scheme 10) Only in the case of lactone **7a** a lower yield of *ca* 55 % was obtained, but no 1,2-reduction product was observed The explanation for this high selectivity probably is that the ketone function is sterically shielded and as a consequence does not react with the hydride donor in a 1,2-fashion As will be demonstrated in Section 3 4, the ketone function in **7** is also unreactive toward other nucleophiles such as MeLi Under these conditions, no $LiAlH_4$ reduction of the lactone moiety in **7** and the ester function in **1** is observed

Scheme 10



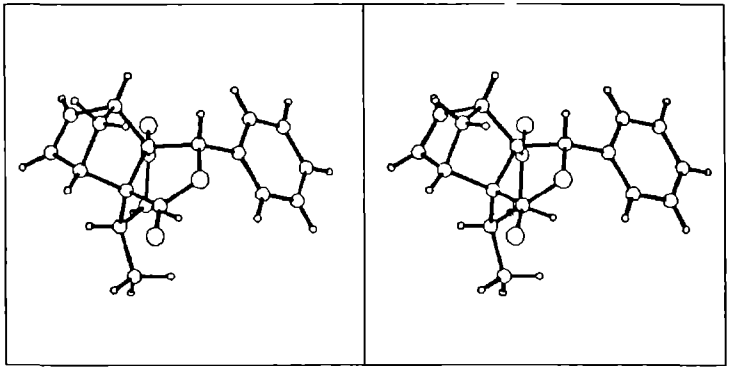
7 **31**

31	R	R_1
a	H	H
b	H	Ph
c	n hexyl	H
d	Me	Me

3 4 REACTIONS OF BRIDGED [4 3 3]OXAPROPELLANES WITH ORGANOMETALLIC REAGENTS

It is well known that MeLi or *n*-BuLi mainly react with enones in a 1,2-addition fashion[30] However, both MeLi and *n*-BuLi react regio- and stereoselectively at the β-position of the enone system in **7** to afford **32** and **33** in high yields (Scheme 11) The high degree of stereoselectivity must be caused by steric shielding of the carbonyl function by the C_9 substituent R_1 It was impossible to assign the stereochemistry at the site of the newly introduced alkyl groups on the basis of ^{1}H-NMR spectroscopy An X-ray diffraction analysis of **32b**[31] revealed the *anti*-position of the methyl group introduced (Fig 3), *i e* pointing away from the norbornene moiety

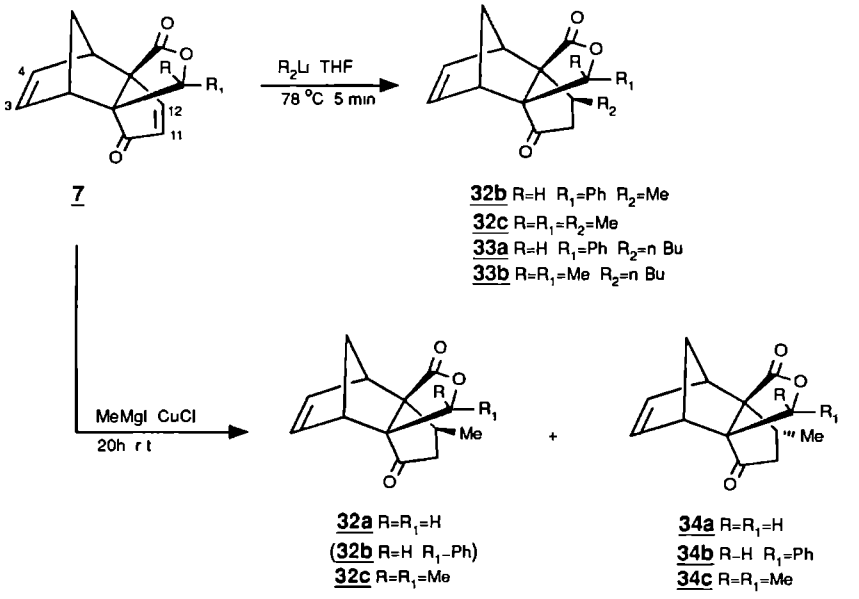
Fig 3



This observation of exclusive *anti*-addition to the enone functions in **7b** and **7i** agrees entirely with the stereochemistry observed for the addition of various nucleophiles to ester **1**[1,24] In lactones **7**, the $C_{8\,9}$ double bond apparently blocks attack of the alkyllithium from the *syn*-face The observation that the enone moiety in **7** is more reactive than in ester **1** suggest anchimeric assistance by the lactone ring Complexation of the organolithium with one of the oxygen atoms of the lactone ring in **7** might place it in a favorable position to attack the enone group in a conjugate manner, thereby promoting this addition to occur with *anti*-stereochemistry

Most unexpectedly, the stereochemical outcome of the conjugate addition of MeMgI in the presence of cuprous chloride did not follow this pattern When **7i** was treated with an excess of MeMgI/CuCl, in a rather slow reaction a diastereomeric mixture of **32c** and **34c** in a molar ratio of 1 3 (^{1}H-NMR) was obtained in a high yield Analysis of the spectra unequivocally established that the major product was the C_{13} epimer of **32c** *viz* **34c** (Scheme 11) Reaction of parent lactone **7a** with MeMgI/CuCl in Et_2O also gave a mixture of the C_{13} epimers **32a** and **34a** (molar ratio 2 1) The Cu(I)-catalyzed Grignard addition to **7b** showed even a higher preference for *syn*-addition Here, no epimer **32b** was isolated This reaction also produced a by-product, that will be discussed below

Scheme 11



7

32b R=H R_1=Ph R_2=Me
32c R=R_1=R_2=Me
33a R=H R_1=Ph R_2=n Bu
33b R=R_1=Me R_2=n Bu

32a R=R_1=H
(**32b** R=H R_1=Ph)
32c R=R_1=Me

34a R=R_1=H
34b R=H R_1=Ph
34c R=R_1=Me

(Scheme 12)

From a merely steric point of view, the reaction of copper(I)-complexed Grignard complex should favor the formation of the *anti*-addition products **32**, because the bulkiness of this reagent is considerably increased in comparison with the normal Grignard reagent[32,33] To understand the experimental finding of predominant *syn*-addition, other factors than steric ones must be operative Formation of the compounds **34** can best be rationalized by assuming a complexation of the binodal d-orbitals of the formed Cu(I)-containing complex with both the $C_{3\text{-}4}$ and $C_{11\ 12}$ double bond of **7**, leading to a transition state that ultimately leads to *syn*-addition As the $C_{3\text{-}4}$ and $C_{11\ 12}$ olefinic moieties are in close proximity (their distance amounts to 2 7-2 8 Å which was deduced from the X-ray structural data of **7b**) such a complexation is quite feasible

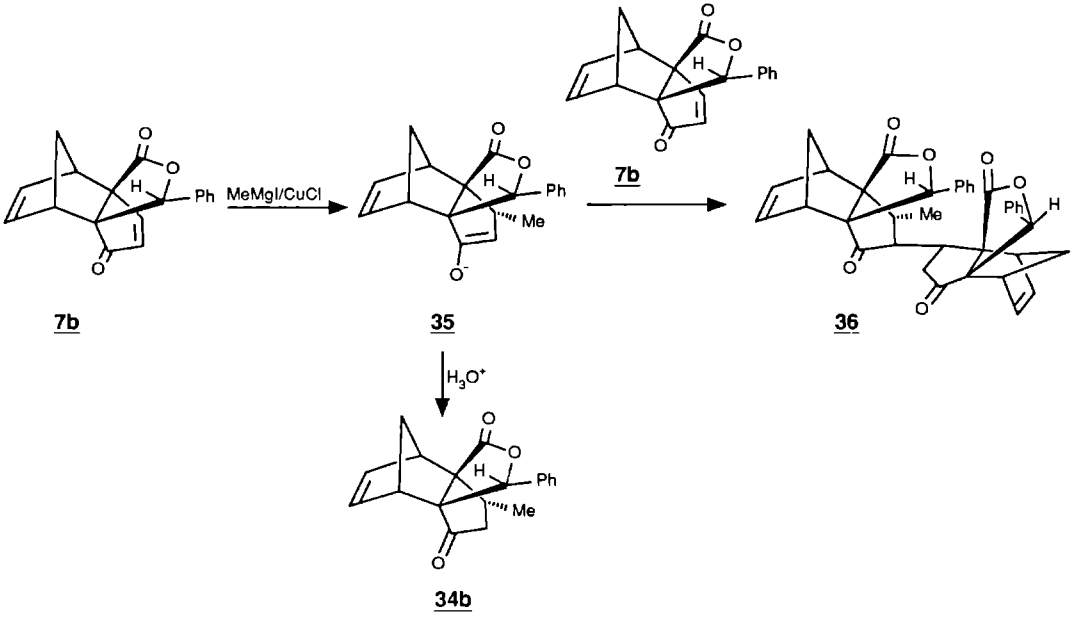
Corey *et al*[34] suggested a similar explanation, involving d-orbital stereoelectronic control, for the stereochemical outcome of SN_2'-displacements by organocuprate reagents Unlike most carbon nucleophiles (*e g* Grignard and organolithium reagents), nucleophilic organocopper(I)reagents contain a filled set of d-orbitals and therefore nucleophilic additions by d^{10}-copper will involve an electron pair in a sterically accessible high energy d orbital The diffuse, binodal orbital is proposed to lead to bidentate overlap in allylic systems and can be described as mainly resulting from the interaction of a copper d-orbital with the LUMO (π^*) of the double bond[35,36]

The tricyclodecadienone ester **1** reacts with Cu(I) complexed Grignard reagents in a highly stereoselective manner[1] (Chapter 1), to give *exo*-β alkylated products exclusively However, it should be mentioned that recently Marchand *et al*[37] reported on the formation of a diastereomeric mixture when

they reacted a tricyclodecadienone carboxylate, which is closely related to **1**, with Me_2CuLi. With substrates **7** the situation with regard to the stereochemistry of the addition of Cu(I) complexed organometallic reagents is still unclear, more studies are needed to uncover the factors that govern the stereochemical course.

As mentioned above the reaction of **7b** with MeMgI/CuCl gave the formation of a by-product. Structure **36** was assigned to this product on basis of ^{1}H-NMR spectroscopy. The orientation of its methyl group is presumably the same as in **34b** as was deduced from a comparison of their ^{1}H-NMR spectra. Its formation is rationalized by invoking addition of enolate **35**, which is formed after initial conjugate addition of the methyl group to **7b**, to the enone moiety of unreacted **7b** (Scheme 12). It seems that the the enone part of **7b** reacts faster with the intermediate enolate **35** than with the MeMgI/CuCl-complex.

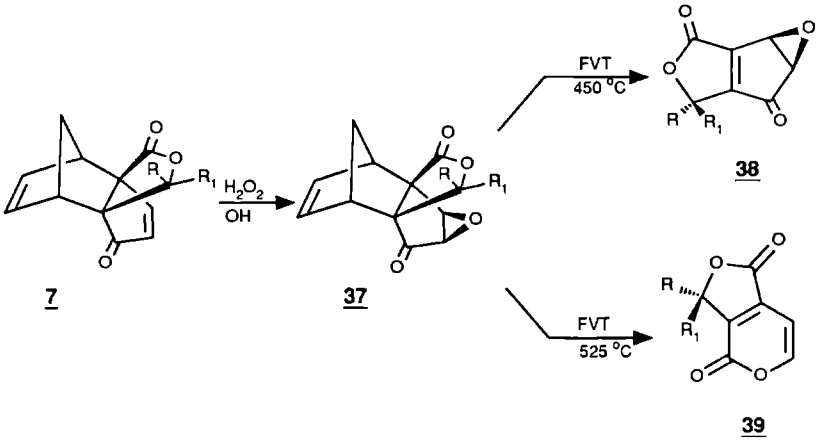
Scheme 12



3.5 NUCLEOPHILIC EPOXIDATION OF BRIDGED [4.3.3]OXAPROPELLANES

Mild selective nucleophilic epoxidation of **7** with H_2O_2 under basic conditions[38] smoothly furnished epoxides **37** in yields ranging from 76-95 %. In all cases studied this nucleophilic epoxidation was completely regio- and stereoselective, presumably affording *anti*-epoxides **37** (Scheme 13). The ease of these epoxidations is quite remarkable and contrasts in fact the difficult conversions of the angularly methylated analogue of **1** (Section 2.3.2).

Scheme 13



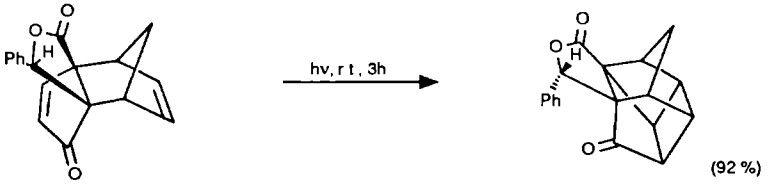
for 37, 38, 39	R	R_1
a	H	H
b	H	Ph
c	t-Bu	H
d	n-hexyl	H
e	$-(CH_2)_5-$	
f	Me	Me

The cycloreversion of the *anti*-epoxides **37** under FVT conditions (450 °C) produced the annelated cyclopentadienone oxides **38** which were characterized by ^{1}H-NMR spectroscopy. When the FVT of **37** was performed at a higher temperature, the compounds **39** were obtained in a yield of *ca.* 50 %, with the exception of **37b**. These products **39** are the result of a further rearrangement of epoxides **38**. Details of both FVT experiments will be given in Chapter 4.

3.6 SYNTHESIS OF AN ANNELATED 1,3-BISHOMOCUBANONE LACTONE

The use of the intramolecular photochemical [2+2]-cycloaddition for the preparation of cage compounds[39,40] is of great synthetic importance. Photocyclization of propellane **7b** proceeded smoothly, furnishing the cage compound **40** in 92 % yield in 3 hours of irradiation in toluene (Scheme 14). Opti-

Scheme 14



(-)-**7b** (-)-**40**

cally active lactone **7b**, (α_D= -11.3°, $CHCl_3$, ee 85 %) was employed (Chapter 5) and therefore an optically active bishomocubanone **40** was obtained (α_D= -35.3°, $CHCl_3$) after flash chromatography. Although the optical purity was not determined, no racemization during the photocyclization process is expected and consequently cage lactone (-)-**40** should be present with an ee≥ 85 %.

This result nicely demonstrates the use of propellanoids 7 for the synthesis of optically active cage compounds[1]. This synthesis deserves further elaboration.

3 7 EXPERIMENTAL PART

General

The remarks given in Section 2 5 also apply here Formaldehyde was dried from P_2O_5 The other aldehydes and ketones were distilled before use

Syntheses

Condensation of **1** *with formaldehyde*

To a stirred soln of diisopropylamine (0 18 g, 1 78 mmol) in dry THF (10 ml) *n*-BuLi (1 2 ml 1 6 M soln in *n*-hexane, 1 92 mmol) was gradually added with a syringe at 0 °C After stirring for 15 min the mixture was cooled to -78 °C and subsequently treated with **1** (300 mg, 1 376 mmol) in 10 ml of THF The resulting yellow soln was allowed to attain -33 °C and excess of CH_2O (g) was passed through the mixture using a N_2 flow Gaseous CH_2O was generated by heating anhydrous formaldehyde at 140-150 °C[14] After acidification (NH_4Cl, 10 % aq), extraction (Et_2O), several washings with water, drying ($MgSO_4$) and concentration *in vacuo*, a yellow syrup (365 mg) was obtained which mainly consisted of a mixture of lactone **7a**, carbinol **6a** and an intractable green polymeric material (^{1}H-NMR) Flash chromatography (Al_2O_3, gradient *n*-hexane /EtOAc = 20/1 to *n*-hexane /EtOAc = 3/1 to EtOH /CH_2Cl_2) successively afforded 74 mg lactone **7a** (Al_2O_3, Rf=0 20, *n*-hexane /EtOAc = 5/1) as a white solid and 91 mg **7a**/**6a** mixture This mixture was converted into **7a** by treatment with *p*-toluenesulfonic acid in CH_2Cl_2 for 2 h at r t The total yield of **7a** was 154 mg (55 %) 7,10-*Dioxo*-8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1,6}$]*trideca*-3,11-*diene* **7a** sublimation > 125 °C (after recrystallization from EtOAc /*n*-hexane = 1/1), ^{1}H-NMR δ 1 98 (br s, 2H, H_{13}), 3 25 (br s, 1H, H_2 or H_5), 3 33-3 44 (m, 1H, H_2 or H_5), 4 25 A of AB (d, ^{2}J=10 4 Hz, 1H, H_9), 4 48 B of AB (d, ^{2}J=10 4 Hz, 1H, H_9), 5 89-6 19 (m, 3H, H_3, H_4, H_{11}), 7 43 (d, ^{3}J=5 6 Hz, 1H, H_{12}), ^{13}C-NMR δ 47 7 (d), 49 1 (t, C_{13}), 49 7 (d, C_2, C_5), 61 9 (s), 68 4 (s, C_1, C_6), 71 2 (t, C_9), 134 5 (d), 134 9 (d), 137 2 (d, C_3, C_4, C_{11}), 159 2 (d, C_{12}), 174 7 (s, C_7), 207 2 (s, C_{10}), IR (KBr) ν 1754 (C=O, lactone), 1710 (C=O, enone), 1575 (C=C, enone), 1190 cm^{-1}, EI/MS m/e 202 (M^+), 174 (M-CO), 115, 66 (C_5H_6), Found C, 71 17, H, 4 98 $C_{12}H_{10}O_3$ requires C, 71 28, H, 4 98 *Ethyl* 6-*hydroxymethyl*-5 *oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-3,8-*diene* 2-*carboxylate* **6a** was characterized by its ^{1}H-NMR-spectrum ^{1}H-NMR δ 1 27 (t, J=7 1 Hz, 3H, CH_3), 1 75 (dt, ^{2}J=9 2 Hz, J=1 3 Hz, 1H, H_{10}), 2 53 (br d, ^{2}J=9 2 Hz, 1H, H_{10}), 3 00 (br s, 1H, H_7), 3 16 (br s, 1H, H_1), 3 98 (s, 2H, C_6-CH_2), 4 22 (q, J=7 1 Hz, 2H, CH_2CH_3), 5 87-6 15 (m, 3H, H_4, H_8, H_9), 7 45 (d, ^{3}J=6 Hz, 1H, H_3)

Attempts to scale up this procedure (5 3 g **1**, 24 3 mmol) gave yields of 20 %, due to concomitant polymerization of CH_2O and decomposition during flash chromatography

7,10 *Dioxo*-anti 9-*phenyl*-8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1,6}$]*trideca*-3,11-*diene* **7b**

LDA was prepared as described for **7a** using diisopropylamine (0 17 g, 1 68 mmol) and *n*-BuLi (1 4

ml, 2 24 mmol) in 10 ml of THF After cooling to -78 °C a soln of **1** (300 mg, 1 376 mmol) in THF (10 ml) was added using a syringe followed, after 15 min, by addition of benzaldehyde (0 15 g, 1 42 mmol) The resulting mixture was allowed to attain 0 °C, and worked up as described for **7a**, to yield 441 mg of crude **7b** Purification by flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1) furnished NMR-pure **7b** (265 mg, 69 %) M p 160-165 °C with concomitant sublimation > 130 °C (after recrystallization from MeOH or EtOAc /*n*-hexane = 1/3) ^{1}H-NMR δ 2 02 (d, J_{AB}=9 9 Hz, 1H, H_{13}), 2 20 (d, J_{AB}=9 9 Hz, 1H, H_{13}), 3 31-3 51 (m, 2H, H_2, H_5), 5 41 (s, 1H, H_9), 5 86 (d, J=5 6 Hz, 1H, H_{11}), 5 87-6 33 (m, 2H, H_3, H_4), 7 04-7 39 (m, 5H, Ph), 7 50 (d, ^{3}J=5 6 Hz, 1H, H_{12}), ^{13}C-NMR δ 47 7 (d), 49 0 (t, C_{13}), 50 1 (d, C_2, C_5), 66 9 (s), 69 6 (s, C_1, C_6), 85 5 (d, C_9), 125 5 (d), 128 5 (d), 128 9, 134 5, 134 8, 135 9 (d), 138 6 (d, C_3, C_4, C_{11}, Ph), 158 0 (d, C_{12}), 175 0 (s, C_7), 204 2 (s, C_{10}), IR (KBr) ν 2980, 1754 (C=O, lactone), 1705 (C=O, enone), 1573 (C=C, unsat), 1420, 1220, 1195 cm^{-1}, EI/MS m/e 278 (M^+), 172 (M-$C_6H_5CH_2O^+$), 115, 66 (C_5H_6), UV (MeOH) λ_{max} 229 nm (3300), Found C, 77 55, H, 5 01 $C_{18}H_{14}O_3$ requires C, 77 68, H, 5 07

7,10-*Dioxo*-syn-9-t-*butyl*-8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1\,6}$]*trideca*-3,11-*diene* **7c**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (2 6 ml 1 6 M, 4 16 mmol), diisopropylamine (0 34 g, 3 37 mmol), **1** (550 mg, 2 52 mmol) and pivalaldehyde (0 26 g, 3 02 mmol) to yield 750 mg crude **7c** as a yellow oil Purification by flash chromatography (Al_2O_3, gradient *n*-hexane /EtOAc = 3/1 to 2/1) afforded NMR-pure **7c** (328 mg, 50 %) as a white solid M p 144-146 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 1 14 (s, 9H, C_9-*t*-Bu), 1 89 (d, J_{AB}=9 6 Hz, 1H, H_{13}), 2 06 (d, J_{AB}=9 6 Hz, 1H, H_{13}), 3 38 (br s, 1H, H_2 or H_5), 3 60 (br s, 1H, H_2 or H_5), 4 16 (s, 1H, H_9), 5 89-6 04 (m, 2H, H_3, H_4), 6 15 (dd, J=5 7 Hz, J=3 0 Hz, 1H, H_{11}), 7 35 (d, ^{3}J=5 7 Hz, 1H, H_{12}), ^{13}C-NMR δ 26 5 (q, CH_3), 34 9 (s, C_9-$C(CH_3)_3$), 45 6 (d), 47 7 (d, C_2, C_5), 50 3 (t, C_{13}), 64 9 (s), 71 1 (s, C_1, C_6), 85 2 (d, C_9), 135 8 (d), 135 9 (d), 137 2 (d, C_3, C_4, C_{11}), 156 4 (d, C_{12}), 174 5 (s, C_7), 205 8 (s, C_{10}), IR (KBr) ν 1755 (C=O, lactone), 1708 (C=O, enone), 1575 (C=C, unsat), 830 cm^{-1}, EI/MS m/e 258 (M^+), 230 (M-CO), 174, 173, 172 (M-*t*-BuCHO), 144 (M-*t*-BuCHO-CO), 115, 66 (C_5H_6), UV (MeOH) λ_{max} 219 nm (4000), Found C, 74 29, H, 7 07 $C_{16}H_{18}O_3$ requires C, 74 40, H, 7 02

7,10-*Dioxo*-syn-9-n *hexyl*-8-*oxatetracyclo*[4 3 3 $1^{2\,5}$ $0^{1\,6}$]*trideca*-3,11-*diene* **7d**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (7 7 ml 1 6 M, 12 3 mmol), diisopropylamine (1 21 g, 12 0 mmol), **1** (2 10 g, 9 63 mmol) and *n*-heptanal (1 57 g, 13 8 mmol) to give 3 4 g of a yellow oil Purification by flash chromatography (silica gel, *n*-hexane /EtOAc = 5/1, Rf = 0 3 with *n*-hexane /EtOAc = 3/1) afforded NMR-pure **7d** (1 0 g, 36 %) M p 81-82 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 0 76-1 87 (m, 13H, C_9-$(CH_2)_5CH_3$), 1 96 (br s, 2H, H_{13}), 3 16 (br s, 1H, H_2 or H_5), 3 33 (br s, 1H, H_2 or H_5), 4 23-4 45 (m, 1H, H_9), 5 89-6 13 (m, 3H, H_3, H_4, H_{11}), 7 45 (d, ^{3}J=5 6 Hz, 1H, H_{12}), IR (KBr) ν 1758 (C=O, lactone), 1710 (C=O, enone), 1572 (C=C, unsat), 1200 cm^{-1}, EI/MS m/e 286, 220 (M-C_5H_6), 172 (M $C_7H_{15}O$), 115, 66 (C_5H_6), Found

C, 75.36; H, 7.75. $C_{18}H_{22}O_3$ requires C, 75.50; H, 7.74.

7,10-*Dioxo*-9-*methyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*trideca*-3,11-*diene* **7e**

The reaction was carried out as described for the preparation of **7b**, using diisopropylamine (0.17 g, 1.68 mmol), *n*-BuLi /*n*-hexane (1.4 ml 1.6 M, 2.24 mmol), **1** (300 mg, 1.376 mmol) and acetaldehyde (0.070 g, 1.59 mmol) to afford a yellow crude oil (416 mg) which predominantly consisted of an equimolar mixture of diastereomeric anti/syn-**7e** (^{1}H-NMR). Flash chromatography (Al_2O_3, *n*-hexane /EtOAc = 5/1, Rf = 0.35) gave **7e** (210 mg, 71 %) as a viscous oil. One of the diastereomers partly decomposed during flash chromatography (diastereomer 2). ^{1}H-NMR diastereomer 1: δ 1.37 (d, J=6.8 Hz, 3H, C_9-Me), 1.82-2.02 (m, 2H, H_{13}), 3.18-3.40 (m, 2H, H_2, H_5), 4.49 (q, J=6.8 Hz, 1H, H_9), 5.87-6.22 (m, 3H, H_3, H_4, H_{11}), 7.50 (d, ^{3}J=5.6 Hz, 1H, H_{12}); diastereomer 2: 1.54 (d, J=6.8 Hz, 3H, C_9-Me), 1.82-2.02 (m, 2H, H_{13}), 3.09-3.40 (m, 2H, H_2, H_5), 4.67 (q, J=6.8 Hz, 1H, H_9), 5.87-6.22 (m, 3H, H_3, H_4, H_{11}), 7.43 (d, ^{3}J=5.6 Hz, 1H, H_{12}); IR (CCl_4): ν 2980, 1765 (C=O, lactone), 1717 (C=O, enone) cm^{-1}; CapGC/EI/MS diastereomer 1: 216 (M^+), 172, 115, 66 (C_5H_6); diastereomer 2: 216 (M^+), 188 (M-CO), 172, 144, 115, 66 (C_5H_6); Found 216.0790. $C_{13}H_{12}O_3$ requires 216.0786.

7,10-*Dioxo*-9-*ethyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*trideca*-3,11-*diene* **7f**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (2.5 ml 1.6 M, 4.00 mmol), diisopropylamine (0.36 g, 3.56 mmol), **1** (580 mg, 2.661 mmol) and propionaldehyde (0.30 g, 5.17 mmol) to yield **7f** (550 mg) as an equimolar diastereomeric mixture (^{1}H-NMR). Flash chromatography (Al_2O_3, *n*-hexane /EtOAc = 2/1, Rf = 0.33) afforded NMR-pure **7f** (500 mg, 82 %) as a white solid. M.p. 115-127 °C (after recrystallization from *n*-hexane /EtOAc = 2/1). ^{1}H-NMR: δ 0.91-2.18 (m, 7H, H_{13}, C_9-Et), 3.09-3.40 (m, 2H, H_2, H_5), 4.16-4.48 (m, 1H, H_9), 5.88-6.22 (m, 3H, H_3, H_4, H_{11}), 7.43/7.47 (2xd, J=5.4 Hz, 1H, H_{12}); IR (KBr): ν 3050, 2970, 1764, 1757 (C=O, lactone), 1703 (C=O, enone), 1570 (C=C, unsat.) cm^{-1}; CapGC/EI/MS diastereomer 1: 230 (M^+), 172 (M-*n*-PrO), 115, 66 (C_5H_6); diastereomer 2: 230 (M^+), 202 (M-CO), 172 (M-*n*-PrO), 144, 115, 66 (C_5H_6); Found 230.0950. $C_{14}H_{14}O_3$ requires 230.0943. Found C, 73.06; H, 6.20. $C_{14}H_{14}O_3$ requires C, 73.03; H, 6.13.

7,10-*Dioxo*-9-n-*propyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*trideca*-3,11-*diene* **7g**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (2.5 ml 1.6 M, 4.00 mmol), diisopropylamine (0.34 g, 3.37 mmol), **1** (560 mg, 2.569 mmol) and butyraldehyde (0.30 g, 4.17 mmol) to produce **7g** (800 mg) as an equimolar diastereomeric mixture (^{1}H-NMR)). Flash chromatography (Al_2O_3, *n*-hexane /EtOAc = 3/1, Rf = 0.25) gave NMR-pure **7g** (504 mg, 80 %) as a viscous oil. ^{1}H-NMR: δ 0.76-1.12 (m, 3H, C_9-$CH_2CH_2CH_3$), 1.15-2.04 (m, 6H, C_9-CH_2CH_2, C_{13}), 3.09-3.40 (m, 2H, H_2, H_5), 4.11-4.56 (m, 1H, H_9), 5.87-6.22 (m, 3H, H_3, H_4, H_{11}), 7.42/7.47 (2xd, J=5.5 Hz, 1H, H_{12}); IR (CCl_4): ν 2960, 1768 (C=O, lactone), 1717 (C=O, enone), 1195 cm^{-1}; CapGC/EI/MS diastereomer 1: 244 (M^+), 172 (M-*n*-BuO), 115, 66 (C_5H_6); diastereomer 2: 244 (M^+),

216 (M CO), 172 (M-*n*-BuO), 144, 115, 66 (C_5H_6), Found 244 1102 $C_{15}H_{16}O_3$ requires 244 1099

7,10-*Dioxo*-9-*i*-*propyl*-8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1,6}$]*trideca*-3,11-*diene* **7h**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (2 6 ml 1 6 M, 4 16 mmol), diisopropylamine (0 34 g, 3 37 mmol), **1** (550 mg, 2 523 mmol) and isobutyraldehyde (0 25 g, 3 47 mmol) to afford **7h** (730 mg) as a diastereomeric mixture in a molar ratio of 1 9 1 (30 % d e , ^{1}H-NMR) Successive purification by flash chromatography and crystallization yielded a 8 1 molar diastereomeric mixture of *syn*/*anti*-**7h** (0 45 g, 73 %) M p dec >105 °C (after recrystallization from *n*-hexane) ^{1}H-NMR *syn*-diastereomer δ 0 82 (d, J=6 6 Hz, 3H, C_9-CHC**H**$_3$), 1 11 (d, J=6 6 Hz, 3H, C_9-CHC**H**$_3$), 1 82-2 29 (m, 3H, C_9-C**H**, H_{13}), 3 16 (br s, 1H, H_2 or H_5), 3 31 (br s, 1H, H_2 or H_5), 4 16 (d, J=4 9 Hz, 1H, H_9), 5 89-6 24 (m, 3H, H_3, H_4, H_{11}), 7 44 (d, J=5 4 Hz, 1H, H_{12}), ^{1}H-NMR *anti*-diastereomer δ 0 82 (d, J=6 6 Hz, 3H, C_9-CHC**H**$_3$), 1 11 (d, J=6 6 Hz, 3H, C_9-CHC**H**$_3$), 1 80-2 29 (m, 3H, C_9 C**H**, H_{13}), 3 31 (br s, 2H, H_2, H_5), 4 00 (d, J=10 9 Hz, 1H, H_9), 5 89-6 24 (m, 3H, H_3, H_4, H_{11}), 7 40 (d, J=5 5 Hz, 1H, H_{12}), IR (KBr) ν 3060, 2980, 1762, 1750 (C=O, lactone), 1705 (C=O, enone), 1570 (C=C, unsat) cm $^{-1}$, CapGC/EI/MS *syn*-diastereomer 244 (M^+), 179, 172, 144, 115, 66 (C_5H_6), *anti*-diastereomer 244 (M^+), 172, 144, 115, 66 (C_5H_6), Found C, 73 79, H, 6 67 $C_{15}H_{16}O_3$ requires C, 73 75, H, 6 60

9,9-*Dimethyl*-7,10-*dioxo*-8-*oxatetracyclo*[4 3 3 $1^{2\,5}$ $0^{1\,6}$]*trideca*-3,11-*diene* **7i**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (1 5 ml 1 6 M, 2 40 mmol), diisopropylamine (0 17 g, 1 68 mmol), **1** (300 mg, 1 38 mmol) and acetone (0 095 g, 1 64 mmol) to yield 370 mg crude **7i** Purification by flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0 20) furnished pure **7i** (227 mg, 72 %) as a white solid M p 131-133 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 1 41 (s, 3H, C_9-Me), 1 57 (s, 3H, C_9-Me), 1 89 (dt, J_{AB}=9 9 Hz, J=1 5 Hz, 1H, H_{13}), 2 20 (dt, J_{AB}=9 9 Hz, J=1 5 Hz, 1H, H_{13}), 3 22-3 37 (m, 2H, H_2, H_5), 5 89 6 22 (m, 3H, H_3, H_4, H_{11}), 7 50 (d, ^{3}J=5 4 Hz, 1H, H_{12}), ^{13}C-NMR δ 24 1 (q, C_9-Me), 28 8 (q, C_9-Me), 46 9 (d), 48 1 (d, C_2, C_5), 50 1 (t, C_{13}), 66 6 (s), 70 9 (s, C_1, C_6), 84 5 (s, C_9), 135 7 (d), 136 5 (d), 137 2 (d, C_3, C_4, C_{11}), 159 0 (d, C_{12}), 174 0 (s, C_7), 206 8 (s, C_{10}), IR (CCl_4) ν 2980, 1765 (C=O, lactone), 1712 (C=O, enone) cm $^{-1}$, EI/MS m/e 230 (M^+), 202 (M-CO), 66 (C_5H_6), UV (MeOH) λ_{max} 220 nm (4300), Found 230 0939 $C_{14}H_{14}O_3$ requires 230 0943, Found C, 73 14, H, 6 22 $C_{14}H_{14}O_3$ requires C, 73 03, H, 6 13

7,10 *Dioxo*-8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1\,6}$]*trideca* 3,11-*dien*-9-*spirocyclohexane* **7j**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (1 3 ml 1 6 M, 2 08 mmol), diisopropylamine (0 17 g, 1 68 mmol), **1** (300 mg, 1 376 mmol) and cyclohexanone (0 162 g, 1 65 mmol) to yield 483 mg crude **7j** Purification by flash chromatography (silica gel, *n* hexane /EtOAc = 3/1, Rf = 0 27) furnished pure **7j** (224 mg, 60 %) as a white solid M p 163-165 °C with concomitant sublimation > 120 °C (after recrystallization from MeOH) ^{1}H-NMR δ 1 07-2 24

(m, 12H, C_9-C(CH_2)$_5$, H_{13}), 3.22-3.38 (m, 2H, H_2, H_5), 5.89-6.20 (m, 3H, H_3, H_4, H_{11}), 7.47 (d, ^{3}J=5.5 Hz, 1H, H_{12}); ^{13}C-NMR: δ 21.5 (t), 21.8 (t), 24.5 (t), 32.3 (t), 37.1 (t, C_9-C(CH_2)$_5$), 45.9 (d), 47.7 (d, C_2, C_5), 50.2 (t, C_{13}), 67.6 (s), 70.7 (s, C_1, C_6), 86.0 (s, C_9), 135.9 (d), 136.5 (d), 137.6 (d, C_3, C_4, C_{11}), 159.1 (d, C_{12}), 174.7 (s, C_7), 208.0 (s, C_{10}); IR (KBr): ν 2940, 1752 (C=O, lactone), 1706 (C=O, enone), 1570 (C=C, unsat.) cm^{-1}; EI/MS: m/e 270 (M^+), 172 (M-$C_6H_{10}O$), 144 (M-$C_6H_{10}O$-CO), 115, 66 (C_5H_6); Found C, 75.53; H, 6.79. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71.

12-{7-(8-*Carboethoxy*-syn-10-*hydroxytricyclo*[5.2.1.0^{2,6}]*deca*-3,8-*dienyl*)}-7,10-*dioxo*-syn-9-t-*butyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*trideca*-3-*ene* **21**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (10.0 ml 1.6 M, 16.0 mmol), diisopropylamine (1.2 g, 11.9 mmol), **1** (2.00 g, 9.174 mmol) and pivalaldehyde (1.0 g, 11.6 mmol) to yield 2.6 g crude white solid which was contaminated with some starting ester **1**. Recrystallization from *n*-hexane/EtOAc = 10/1 gave NMR-pure **21** (620 mg, 14 %). Subsequent re-crystallizations from EtOH afforded suitable crystals for an X-ray diffraction study. M.p. 198-201 °C. ^{1}H-NMR: δ 1.09 (s, 9H, C_9-*t*-Bu), 1.36 (t, J=7 Hz, 3H, OCH_2CH_3), 1.54 (br d, J_{AB}=9 Hz, 1H, H_{13}), 1.77 (br d, J_{AB}=9 Hz, 1H, H_{13}), 1.96-2.76 (m, 7H), 2.89-3.38 (m, 3H), 3.54 (br s, 1H), 3.67-3.93 (m, 1H), 4.07-4.49 (m, 3H, H_9, OCH_2), 5.20-5.40 (m, 1H), 5.44-5.61 (m, 1H), 6.20-6.33 (m, 1H), 6.44-6.61 (m, 2H, H_3, H_4, $H_{3'}$, $H_{4'}$, $H_{9'}$); IR (KBr): ν 3600-3300 (OH), 2980, 1755 (C=O, lactone), 1732 (C=O, ketone), 1705 (C=O, ester, unsat.), 1590 (C=C, unsat.), 1370, 1095 cm^{-1}; EI/MS: m/e 478 (M^+), 432 (M-HOEt), 414 (M-HOEt-H_2O), 66 (C_5H_6), 57 (*t*-Bu^+); CI/MS: m/e 479 (M+1), 461 (M-H_2O), 433, 413 (M-$C_5H_5^+$), 367, 67; Found 479.2441. $C_{29}H_{35}O_6$ requires 479.2434. Found C, 71.95; H, 7.23. $C_{29}H_{34}O_6$ requires C, 72.78; H, 7.16.

7,10-*Dioxo*-anti-12-(2-*oxocyclohexyl*)-9-*spirocyclohexane*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*trideca*-3-*ene* **22**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (6.0 ml 1.6 M, 9.6 mmol), diisopropylamine (0.80 g, 7.92 mmol), **1** (1.20 g, 5.50 mmol) and cyclohexanone (1.00 g, 10.2 mmol) to yield a mixture of 3.08 g crude **22** and a small amount of **1**. This mixture was purified by crystallization from *n*-hexane. The remaining mother liquors were purified by flash chromatography (silica gel, *n*-hexane /EtOAc = 2/1, Rf = 0.40) to produce NMR-pure **22** (1.15 g, 57 %) as a white solid. M.p. 172-173 °C. ^{1}H-NMR: δ 1.10-2.82 (m, 24H, C_9-C(CH_2)$_5$, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$, H_{11}, H_{12}, H_{13}), 3.24-3.38 (m, 1H, H_2 or H_5), 3.40-3.53 (m, 1H, H_2 or H_5), 6.18 (ddd, J=5.7 Hz, J=3.0 Hz, J=0.6 Hz, 1H, H_3 or H_4), 6.47 (dd, J=5.7 Hz, J=3.0 Hz, 1H, H_3 or H_4); IR (KBr): ν 2940, 1747 (C=O, lactone), 1735, 1715 (C=O), 1195 cm^{-1}; EI/MS: m/e 368 (M^+), 303 (M-$C_5H_5^+$), 285 (M-$C_5H_5^+$-H_2O), 205 (M-$C_5H_5^+$-$C_6H_{10}O$), 66 (C_5H_6); Found C, 74.94; H, 7.71. $C_{23}H_{28}O_4$ requires C, 74.97; H, 7.66.

2,6-*Dioxo*-8-(2-*oxocyclohexyl*)-3-*oxabicyclo*[3.3.0]*oct*-1(5)-*en*-4-*spirocyclohexane* **23**

Flash vacuum thermolysis (FVT) of **22** (206 mg, 0.560 mmol) (oven temp.: 520 °C, p: 2.10^{-2} torr,

preheating temp.: 120-155 °C, cold trap temp.: -78 °C) slowly gave **23** (154 mg, 91 %) as a NMR-pure white solid (*Cf.* Appendix of Chapter 2). M.p. 144-146 °C (after recrystallization from *n*-hexane /CH_2Cl_2 = 10/1). ^{1}H-NMR: δ 1.22-2.54 (m, 18H, $H_{2'}$, $H_{3'}$, $H_{4'}$, $H_{5'}$, $H_{6'}$, $H_{3''}$, $H_{4''}$, $H_{5''}$, $H_{6''}$), 2.58 A of ABX (dd, ^{2}J=19.5 Hz, J=2.1 Hz, 1H, H_7), 3.18 B of ABX (dd, ^{2}J=19.5 Hz, J=6.3 Hz, 1H, H_7), 2.91-3.19 (m, 1H, $H_{1''}$), 3.53-3.69 X of ABX (m, 1H, H_8); IR (KBr): ν 2860, 1754 (C=O, lactone), 1705 (C=O), 1220 cm^{-1}; EI/MS: m/e 302 (M^+), 284 (M-H_2O), 258 (M-H_2O-CO), 205 (M-$C_6H_9O^+$); UV (MeOH): λ_{max} 237 nm (9500); Found C, 71.47; H, 7.23. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33.

Ethyl 5-*oxo*-exo-3-(2-*oxocyclopentyl*)-endo-*tricyclo*[5.2.1.0^{2,6}]*dec*-8-*ene* 2-*carboxylate* **24**

The reaction was carried out as described for the preparation of **7b**, using *n*-BuLi (10.0 ml 1.6 M, 16.0 mmol), diisopropylamine (1.2 g, 11.9 mmol), **1** (1.00 g, 4.59 mmol) and cyclopentanone (1.30 g, 15.5 mmol) to yield 2.2 g crude oil which contained a small amount of **24**. Subsequent purification by flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0.15) produced **24** (300 mg) which was contaminated with cyclopentanone dimers. Finally, crystallization from *n*-hexane afforded pure **24** (20 mg, 1 %). M.p. 26-30 °C. ^{1}H-NMR: δ 1.32 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.44-2.51 (m, 10H, $H_{3'}$, $H_{4'}$, $H_{5'}$, H_4, H_{10}), 2.60-2.82 (m, 2H, $H_{2'}$, H_3), 3.07-3.22 (m, 1H, H_7), 3.30 (d, J=5.1 Hz, 1H, H_6), 3.33-3.47 (m, 1H, H_1), 4.27 (q, J=7.1 Hz, 2H, OCH_2), 6.16 (dd, J=5.4 Hz, J=2.7 Hz, 1H, H_8 or H_9), 6.34 (dd, J=5.4 Hz, J=2.7 Hz, 1H, H_8 or H_9); IR (CCl_4): ν 1740, 1725, 1175, 1150 cm^{-1}; EI/MS: m/e 302 (M^+), 256 (M-HOEt), 237 (M-$C_5H_5^+$), 191 (M-$C_5H_5^+$-HOEt), 84 (C_5H_8O), 66 (C_5H_6); CI/MS: m/e 303 (M^++1), 237 (M+1-C_5H_6), 191, 151, 85; Found 302.1525. $C_{18}H_{22}O_4$ requires 302.1518. *Cyclopentanone dimer*: ^{1}H-NMR: δ 1.80-2.40 (m, 14H); IR (CCl_4): ν 2960, 1745, 1150 cm^{-1}; EI/MS: m/e 150 (M^+), 84 (C_5H_8O); Found 150.1043. $C_{10}H_{14}O$ requires 150.1045.

Ethyl 3-*oxo*-5-(2-*oxocyclopentyl*)-3-*oxocyclopentene* 1-*carboxylate* **25**

FVT (oven temp.: 525 °C, p: 2.10^{-2} torr, preheating temp.: 80-100 °C, cold trap temp.: -78 °C) of **24** (7 mg, 0.047 mmol) gave **25** (6 mg, 100 %) as a NMR-pure oil. ^{1}H-NMR: δ 1.34 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.44-2.60 (m, 6H, $H_{3'}$,$H_{4'}$, $H_{5'}$), 2.15 A of ABX (dd, J_{AB}=18.9 Hz, J_{AX}=3.0 Hz, 1H, H_4), 2.73 B of ABX (dd, J_{AB}=18.9 Hz, J_{BX}=6.7 Hz, 1H, H_4), 2.56-2.96 (m, 1H, $H_{2'}$), 3.56 (dddd, J_{AX}=6.7 Hz, J=3.6 Hz, J_{BX}=3.0 Hz, ^{4}J=2.2 Hz, 1H, H_5), 4.31 (q, J=7.0 Hz, 2H, OCH_2), 6.75 (d, ^{4}J=2.2 Hz, 1H, H_2); IR (CCl_4): ν 1735-1715, 1605, 1210 cm^{-1}; EI/MS: m/e 236 (M^+), 190 (M-HOEt), 163, 162 (M-CO-HOEt); Found 236.1059. $C_{13}H_{16}O_4$ requires 236.1049.

Ethyl 5-*oxo*-endo-*tricyclo*[5.2.1.0^{2,6}]*decane* 2-*carboxylate* **26**

A soln of **1** (95 mg, 0.436 mmol) in EtOH (10 ml) was hydrogenated at r.t. for 5 min with Pd/C as catalyst. Filtration and subsequent flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3, Rf = 0.3) gave **26** (91 g, 94 %). ^{1}H-NMR: δ 1.27 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.33-1.71 (m, 7H, H_3, H_8, H_9, H_{10}), 1.89-2.82 (m, 5H, H_1, H_3, H_4, H_7), 3.09 (br d, J=5.8 Hz, 1H, H_6), 4.15 (q, J=7.2 Hz, 2H, OCH_2); EI/MS: m/e 222 (M^+); Found 222.1251. $C_{13}H_{18}O_3$ requires 222.1256.

Ethyl 5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-3-*ene* 2-*carboxylate* **27**

1 (300 mg, 1 38 mmol) was added to a soln of Et_3SiH (420 mg, 3 62 mmol) in dry THF (20 ml) in a N_2 atmosphere After addition of a catalytic amount of $(Ph_3P)_3Rh(I)Cl$ (12 mg, 0 013 mmol) the resulting soln was heated at reflux for 20 h Subsequent hydrolysis with K_2CO_3 aq for 5 min at r t , extraction with Et_2O (3x), washing with water, drying and concentration *in vacuo*, yielded 480 mg of a 3 1 molar mixture of **27** and **1** containing some impurities These were removed by flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1) The total yield of the mixture was 150 mg (50 %) ^{1}H-NMR δ 1 11-1 71 (m, 7H, OCH_2CH_3, H_{10}, H_8 or H_9), 1 78-2 07 (m, 2H, H_8 or H_9), 2 62-2 89 (m, 2H, H_1, H_7), 3 09 (d, J=5 4 Hz, 1H, H_6), 4 18 (q, J=7 Hz, 2H, OCH_2), 6 05 (d, J=5 7 Hz, 1H, H_4), 7 56 (d, J=5 7 Hz, 1H, H_3), CapGC/EI/MS m/e 220 (M^+), 192 (M-CO), 164 (M-HOEt), 154, Found 220 1090 $C_{13}H_{16}O_3$ requires 220 1099

Ethyl 5-*oxo*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* 2-*carboxylate* **28**

To a suspension of $LiAlH_4$ (0 40 g, 10 6 mmol) in dry THF (25 ml) at -78 °C was added, in a N_2 flow, a soln of **1** (1 00 g, 4 59 mmol) in THF (10 ml) using a syringe After 10 min, an excess of acetone was added to the mixture, followed by 3 % HCl aq Extraction with Et_2O (3x), several washings (H_2O), drying ($MgSO_4$) and concentration *in vacuo* produced 1 07 g of an oil Purification by flash chromatography (silica gel, *n*-hexane /EtOAc = 2/1, Rf = 0 37, H_2SO_4) gave NMR-pure **28** (510 mg, 51 %, purity by CapGC >98 %) and **29** (200 mg, 20 %) **28** ^{1}H-NMR δ 1 29 (t, J=7 1 Hz, 3H, OCH_2CH_3), 2 00 (br s, 2H, H_{10}), 2 00-2 60 (m, 4H, H_3, H_4), 3 13-3 44 (m, 3H, H_1, H_6, H_7), 4 22 (q, J=7 1 Hz, 2H, OCH_2), 6 15-6 37 (m, 2H, H_8, H_9), ^{13}C-NMR δ 14 0 (q, CH_3), 27 7 (t, C_3), 40 6 (t, C_4), 46 3 (d), 51 0, 51 1(d,t, C_1, C_7, C_{10}), 58 2 (s, C_2), 58 8 (d, C_6), 60 9 (t, OCH_2), 135 2 (d), 138 3 (d, C_8, C_9), 177 0 (s, C_2-CO), 220 0 (s, C_5), IR (CCl_4) ν 2980, 1735, 1725 (C=O), 1230 cm^{-1}, EI/MS m/e 220 (M^+), 192 (M-CO), 175 ($M-OEt^+$), 155 ($M-C_5H_5^+$), 66 (C_5H_6), Found 221 1168 (M+1). $C_{13}H_{16}O_3$ requires 221 1178 (M+1)

Ethyl anti-10-*hydroxy*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*deca*-3,8-*diene* 8-*carboxylate* **29**

Ester **1** (290 mg, 1 330 mmol) was added to a soln of freshly prepared $LiAlH(OMe)_3$ (330 mg, 2 58 mmol) in 10 ml of THF and stirred for 6 h After work-up according to the procedure described for the synthesis of **28**, **29** (230 mg, 79 %) was obtained as a crude oil ^{1}H NMR δ 1 29 (t, J=7 1 Hz, 3H, OCH_2CH_3), 1 49-1 56 (m, 3H, H_5, H_6), 2 80-3 31 (m, 3H), 3 38-3 72 (m, 1H), 3 87 (br s, 1H, H_1, H_2, H_7, H_{10}, C_{10} OH), 4 18 (q, J=7 Hz, 2H, OCH_2), 5 50 (s, 2H, H_3, H_4), 6 77 (d, J=3 7 Hz, 1H, H_9), IR (CCl_4) ν 3620 (OH), 3480 (OH), 3040, 2980, 1710 (C=O), 1590 (C=C, unsat), 1265, 1070 cm^{-1}, CI/MS m/e 221 (M^++1), 203 (M+1-H_2O), 155 (M+1-C_5H_6), 67, 66 (C_5H_6), Found 221 1177 $C_{13}H_{17}O_3$ requires 221 1178

7,10-*Dioxo*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **31a**

The same procedure as described for the synthesis of **28** was applied using **7a** (144 mg, 0.713 mmol) and $LiAlH_4$ (38 mg, 1.00 mmol) in THF (5 ml) to afford crude **31a** (152 mg). Purification by flash chromatography (silica gel, *n*-hexane /EtOAc = 2/1, Rf = 0.25) gave NMR-pure **31a** (80 mg, 55 %) as a white solid (100 % purity by CapGC). M.p. dec. >155 °C with concomitant sublimation > 120 °C (after recrystallization from n-hexane). ^{1}H-NMR: δ 1.62-2.82 (m, 6H, H_{11}, H_{12}, H_{13}), 3.22 (br s, 1H, H_2 or H_5), 3.38 (br s, 1H, H_2 or H_5), 4.16 A of AB (d, ^{2}J=10.5 Hz, 1H, H_9), 4.41 B of AB (d, ^{2}J=10.5 Hz, 1H, H_9), 6.30 (ddd, J=5.4 Hz, J=3.0 Hz, J=0.7 Hz, 1H, H_3 or H_4), 6.42 (dd, J=5.4 Hz, J=3.0 Hz, 1H, H_3 or H_4); IR (KBr): ν 2978, 1761 (C=O, lactone), 1727 (C=O, ketone), 1137, 1020 cm^{-1}; EI/MS: m/e 204 (M^+), 176 (M-CO), 162 (M-$COCH_2^+$), 139 (M-$C_5H_5^+$), 66 (C_5H_6); Found 204.0780. $C_{12}H_{12}O_3$ requires 204.0786.

7,10-*Dioxo*-anti-9-*phenyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **31b**

The same procedure as described for the synthesis of **28** was applied using **7b** (1.04 g, 3.741 mmol) and $LiAlH_4$ (0.35 g, 9.23 mmol) in THF (10 ml) to afford NMR-pure **31b** (1.04 g, 99 %) as a white solid (purity by CapGC 100 %). M.p. 155-164 °C with concomitant sublimation > 150 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.49-2.53 (m, 6H, H_{11}, H_{12}, H_{13}), 3.29-3.44 (m, 2H, H_2, H_5), 5.35 (s, 1H, H_9), 6.13-6.42 (m, 2H, H_3, H_4), 7.11-7.47 (m, 5H, Ph); ^{13}C-NMR: δ 25.1 (t, C_{12}), 42.5 (t, C_{11}), 48.4 (t, C_{13}), 50.4 (d), 51.2 (d, C_2, C_5), 63.2 (s), 71.9 (s, C_1, C_6), 85.8 (d, C_9), 125.2 (d), 128.4 (d), 128.5 (d), 135.8 (s), 135.8 (d), 137.8 (d, C_3, C_4, Ph), 179.8 (s, C_7), 213.5 (s, C_{10}); IR (KBr): ν 2980, 1767 (C=O, lactone), 1740 (C=O, ketone), 1451, 1182, 1130, 1020 cm^{-1}; EI/MS: m/e 280 (M^+), 215 (M-$C_5H_5^+$), 174 (M-C_6H_5CHO), 104, 66 (C_5H_6); Found 280.1095. $C_{18}H_{16}O_3$ requires 280.1099.

7,10-*Dioxo*-syn-9-n-*hexyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **31c**

The same procedure as described for the synthesis of **28** was applied using **7d** (320 mg, 1.12 mmol) and $LiAlH_4$ (180 mg, 4.75 mmol) in THF (10 ml) to afford NMR-pure **31c** (311 mg, 97 %) as a white solid after flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0.3). M.p. 60-61.5 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 0.77-1.00 (m, 3H, CH_3), 1.11-1.91 (m, 13H, C_9-$(CH_2)_5$, H_{12}, H_{13}), 1.96-2.54 (m, 3H, H_{11}, H_{12}), 3.14 (br s, 1H, H_2 or H_5), 3.32 (br s, 1H, H_2 or H_5), 4.11-4.28 (m, 1H, H_9), 6.20 (dd, J=5.4 Hz, J=3.2 Hz, 1H, H_3 or H_4), 6.34 (dd, J=5.4 Hz, J=3.2 Hz, 1H, H_3 or H_4); IR (KBr): ν 1760 (C=O, lactone), 1735 (C=O, ketone), 1462 cm^{-1}; EI/MS: m/e 288 (M^+), 223 (M-$C_5H_5^+$), 66 (C_5H_6); Found C, 75.07; H, 8.45. $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39.

9,9-*Dimethyl*-7,10-*dioxo*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **31d**

The same procedure as described for the synthesis of **28** was applied using **7i** (935 mg, 4.065 mmol) and $LiAlH_4$ (400 mg, 10.6 mmol) in THF (10 ml) to afford NMR-pure **31d** (940 mg, 100 %) as a white solid. M.p. 173-177 °C with concomitant sublimation > 130 °C (after recrystallization from

n-hexane /CH_2Cl_2 = 20/1). ^{1}H-NMR: δ 1.37 (s, 3H, C_9-Me), 1.53 (s, 3H, C_9-Me), 1.66 (dt, J_{AB}=10 Hz, J=1.5 Hz, 1H, H_{13}), 1.82 (dt, J_{AB}=10 Hz, J=1.5 Hz, 1H, H_{13}), 1.89-2.78 (m, 4H, H_{11}, H_{12}), 3.22-3.39 (m, 2H, H_2, H_5), 6.14-6.27 (m, 1H, H_3 or H_4), 6.31-6.45 (m, 1H, H_3 or H_4); ^{13}C-NMR: δ 23.6 (q, C_9-Me), 24.5 (t, C_{12}), 29.3 (q, C_9-Me), 42.6 (t, C_{11}), 48.9 (d or t), 49.1 (d or t), 50.8 (d, C_2, C_5, C_{13}), 64.3 (s), 72.2 (s, C_1, C_6), 84.2 (s, C_9), 136.2 (d), 139.4 (d, C_3, C_4), 179.0 (s, C_7), 218.1 (s, C_{10}); IR (KBr): ν 2970, 2880, 1757 (C=O, lactone), 1726 (C=O, ketone), 1460, 1390, 1290, 1120 cm^{-1}; EI/MS: m/e 232 (M^+), 217 (M-CH_3^+), 167 (M-$C_5H_5^+$), 66 (C_5H_6); Found C, 72.21; H, 6.83. $C_{14}H_{16}O_3$ requires C, 72.39; H, 6.94.

7,10-*Dioxo*-anti-12-*methyl*-anti-9-*phenyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **32b**

To a soln of **7b** (2.40 g, 8.63 mmol) in THF (20 ml) was added MeLi (6.5 ml 1.6 M in Et_2O, 10.4 mmol) at -78 °C. A white-yellow precipitate was formed. After stirring for 10 min, an excess of NH_4Cl (10 % aq) was added and the resulting mixture was allowed to attain r.t. Extraction with Et_2O (3x), followed by several washings with H_2O, drying ($MgSO_4$) and concentration *in vacuo* yielded a viscous yellow oil (2.8 g). Subsequent flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1) gave NMR-pure **32b** (2.32 g, 92 %) as a white solid. M.p. 129.5-131 °C (after recrystallization from *n*-hexane /EtOAc = 3/1). ^{1}H-NMR: δ 1.28 (d, J=6.0 Hz, 3H, C_{12}-Me), 1.51-2.33 (m, 5H, H_{11}, H_{12}, H_{13}), 3.27-3.42 (m, 2H, H_2, H_5), 5.33 (s, 1H, H_9), 6.27 (t, J=2.0, 2H, H_3, H_4), 7.18-7.44 (m, 5H, Ph); ^{13}C-NMR (200 MHz): δ 17.9 (q, C_{12}-Me), 32.4 (d, C_{12}), 48.6 (t, C_{11}), 50.1 (d), 50.7 (d, C_2, C_5), 51.6 (t, C_{13}), 66.5 (s), 73.3 (s, C_1, C_6), 84.6 (d, C_9), 125.1 (d), 128.1 (d), 128.3 (d), 135.3 (s), 135.8 (d), 137.8 (d, C_3, C_4, Ph), 176.6 (s, C_7), 211.1 (s, C_{10}); IR (KBr): ν 2955, 1760 (C=O, lactone), 1735 (C=O, ketone), 1195 cm^{-1}; EI/MS: m/e 294 (M^+), 229 (M-$C_5H_5^+$), 188 (M-C_6H_5CHO), 66 (C_5H_6); Found C, 77.36; H, 6.14. $C_{19}H_{18}O_3$ requires C, 77.53; H, 6.16.

9,9-*Dimethyl*-7,10-*dioxo*-anti-12-*methyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **32c**

The same procedure as described for the preparation of **32b** was employed using **7i** (1.36 g, 5.913 mmol) and MeLi (4.8 ml 1.6 M, 7.68 mmol) in THF (20 ml). A viscous oil (1.5 g) was produced which was purified by flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0.25, H_2SO_4) to afford NMR-pure **32c** (1.15 g, 79 %). M.p. 150 °C with concomitant sublimation > 120 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.24 (d, J=7.0 Hz, 3H, C_{12}-Me), 1.40 (s, 3H, C_9-Me), 1.53 (s, 3H, C_9-Me), 1.71 (br d, J=1.6 Hz, 2H, H_{13}), 1.93-2.80 (m, 3H, H_{11}, H_{12}), 3.22-3.40 (m, 2H, H_2, H_5), 6.15-6.30 (m, 1H, H_3 or H_4), 6.30-6.44 (m, 1H, H_3 or H_4); IR (KBr): ν 2970, 2880, 1755 (C=O, lactone), 1725 (C=O, ketone), 1385, 1120 cm^{-1}; EI/MS: m/e 246 (M^+), 231 (M-CH_3^+), 181 (M-$C_5H_5^+$), 66 (C_5H_6); Found C, 73.17; H, 7.43. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37.

Anti-12-n-*butyl*-7,10-*dioxo*-anti-9-*phenyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **33a**

The same procedure as described for the preparation of **32b** was employed, using **7b** (2.10 g, 7.55 mmol) and *n*-BuLi (6.14 ml 1.6 M, 9.82 mmol) to produce a viscous oil (2.9 g). Purification by flash

chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0 37) afforded NMR-pure **33a** (2 23 g, 88 %) which failed to solidify ^{1}H-NMR δ 0 78 2 22 (m, 14H, C_{12}-*n*-Bu, H_{11}, H_{12}, H_{13}), 3 31-3 42 (m, 2H, H_2, H_5), 5 33 (s, 1H, H_9), 6 27 (t, J=1 8 Hz, 2H, H_3, H_4), 7 20-7 42 (m, 5H, C_9-Ph), ^{13}C NMR (200 MHz) δ 13 3 (q), 22 0 (t), 30 1 (t), 32 1 (t, C_{12}-*n*-Bu), 38 1 (d, C_{12}), 48 5, 49 9, 50 3 (2C, d,d,t,t, C_2, C_5, C_{11}, C_{13}), 65 9 (s), 72 9 (s, C_1, C_6), 84 4 (d, C_9), 125 5 (d), 128 1 (d, 2C), 135 3 (s), 135 9 (d), 137 7 (d, C_3, C_4, Ph), 176 7 (s, C_7), 211 0 (s, C_{10}), IR (CCl_4) ν 2950, 2920, 1775 (C=O, lactone), 1740 (C=O, ketone), 1190, 1027 cm^{-1}, EI/MS m/e 336 (M^+), 271 (M $C_5H_5^+$), 230 (M C_6H_5CHO), 66 (C_5H_6), Found 336 1707 $C_{22}H_{24}O_3$ requires 336 1725

Anti-12-n-*butyl*-9,9-*dimethyl*-7,10 *dioxo* 8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1,6}$]*tridec*-3-*ene* **33b**

The same procedure as described for the preparation of **32b** was employed, using **7i** (1 38 g, 6 00 mmol) and *n*-BuLi (4 5 ml 1 6 M, 7 20 mmol) in THF (20 ml) to produce NMR-pure **33b** (1 60 g, 93 %) as a white solid M p 123-125 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 0 78 2 15 (m, 18H, C_{12} *n*-Bu, C_9 $(CH_3)_2$ (δ=1 38, δ=1 51 respectively), H_{11}, H_{12}, H_{13}), 2 16 A of ABX (dd, J_{AB}=20 Hz, J_{AX}=6 Hz, 1H, H_{11}), 2 51 B of ABX (dd, J_{AB}=20 Hz, J_{BX}=10 Hz, 1H, H_{11}), 3 22 3 40 (m, 2H, H_2, H_5), 6 14 6 43 (m, 2H, H_3, H_4), ^{13}C-NMR (200 MHz) δ 13 3 (q), 21 8 (t), 23 8 (q, C_9-Me), 27 8 (q, C_9-Me), 30 0 (t), 32 5 (t, C_{12}-*n*-Bu), 36 7 (d, C_{12}), 48 5, 48 7, 49 2 (d,t,t), 51 2 (d, C_2, C_5, C_{11}, C_{13}), 68 1 (s), 73 4 (s, C_1, C_6), 82 8 (s, C_9), 136 7 (d), 139 0 (d, C_3, C_4), 176 8 (s, C_7), 217 8 (s, C_{10}), IR (KBr) ν 2960, 1755 (C=O, lactone), 1727 (C=O, ketone), 1255 cm^{-1}, EI/MS m/e 288 (M^+), 223 (M $C_5H_5^+$), 66 (C_5H_6), Found C, 74 71, H, 8 38 $C_{18}H_{24}O_3$ requires C, 74 97, H, 8 39

Cu(I)-catalyzed Grignard addition of MeMgI to **7a**

Mg (40 mg, 1 65 mmol) was crushed in a mortar and added to dry Et_2O (10 ml) in a N_2 atmosphere at 0 °C CuCl (25 mg, 0 25 mmol) was added to the mixture, followed by addition of MeI (200 mg, 1 41 mmol) in Et_2O (5 ml) After stirring for 45 min a soln of **7a** (200 mg, 0 99 mmol) in 5 ml Et_2O was added and the reaction mixture was stirred for 15 h at r t Subsequently, the mixture was quenched with an excess of NH_4Cl aq, extracted twice with Et_2O, washed (H_2O), dried and concentrated to leave crude **32a**/**34a** (180 mg) which contained some **7a** Flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1) gave a mixture of 7,10-*dioxo*-anti/syn-12-*methyl*-8 *oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1,6}$]*tridec*-3 *ene* **32a**/**34a** (95 mg, 44%) in a molar ratio of 2 1 (^{1}H-NMR) ^{1}H-NMR (mixture) δ 1 18 (d, J=6 3 Hz, 3H, C_{12}-Me, probably *anti*-diastereomer), 1 27 (d, J=6 3 Hz, 3H, C_{12}-Me, probably *syn*-diastereomer), 1 55-1 78 (m, 2H, H_{13}), 2 00 2 67 (m, 3H, H_{11}, H_{12}), 3 07-3 40 (m, 2H, H_2, H_5), 4 00 4 51 (m, 2H, H_9), 6 09 6 53 (m, 2H, H_3, H_4), CapGC/EI/MS **32a** 218 (M^+), 190, 153 (M-$C_5H_5^+$), 115, 66 (C_5H_6), **34a** 218 (M^+), 190, 153 (M-$C_5H_5^+$), 115, 66 (C_5H_6)

7,10 *Dioxo*-syn-12-*methyl* anti 9 *phenyl* 8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1,6}$]*tridec*-3-*ene* **34b**

The same procedure as described for the preparation of **32a**/**34a** was employed, using Mg (55 mg, 2 26 mmol), CuCl (25 mg, 0 25 mmol), MeI (200 mg, 1 41 mmol) and **7b** (90 mg, 0 32 mmol) to yield

pure **34b** (93 mg, 98 %) after flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0.23) as a white solid. M.p. 137-138 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.29 (d, J=6.6 Hz, 3H, C_{12}-Me), 1.69 A of ABX (dd, J_{AB}=19.5 Hz, J_{AX}=11.4 Hz, 1H, H_{11}), 1.84 (s, 2H, H_{13}), 2.24 B of ABX (dd, J_{AB}=19.5 Hz, J_{BX}=9.6 Hz, 1H, H_{11}), 2.49-2.98 (m, 1H, H_{12}), 3.29-3.56 (m, 2H, H_2, H_5), 5.34 (s, 1H, H_9), 6.15 (ddd, J=5.7 Hz, J=4.0 Hz, J=0.6 Hz, 1H, H_3 or H_4), 6.42 (ddd, J=5.7 Hz, J=4.0 Hz, J=0.6 Hz, 1H, H_3 or H_4), 7.15-7.44 (m, 5H, Ph); ^{13}C-NMR (200 MHz): δ 15.8 (C_{12}-CH_3), 33.4 (C_{11}), 48.1, 49.1, 50.1, 52.9 (C_2, C_5, C_{12}, C_{13}), 66.3, 73.6 (C_1, C_6), 85.9 (C_9), 125.6, 128.7, 128.8, 136.6, 137.3 (2C, C_3, C_4, Ph), 179.1 (C_7), 214.4 (C_{10}); IR (KBr): ν 2970, 1767 (C=O, lactone), 1736 (C=O, ketone), 1215, 1010 cm^{-1}; EI/MS: m/e 294 (M^+), 229 (M-$C_5H_5^+$), 188 (M-C_6H_5CHO), 66 (C_5H_6); Found 294.1255. $C_{19}H_{18}O_3$ requires 294.1256; Found C, 77.97; H, 6.27. $C_{19}H_{18}O_3$ requires C, 77.53; H, 6.16.

9,9-*Dimethyl*-7,10-*dioxo*-syn-12-*methyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **34c**

The same procedure as described for the preparation of **32a**/**34a** was employed using Mg (140 mg, 5.76 mmol), CuCl (52 mg, 0.53 mmol), MeI (300 mg, 2.11 mmol) and **7i** (120 mg, 0.522 mmol) to yield a diastereomeric mixture of **32c** and **34c** in molar ratio of 1:3 (^{1}H-NMR). Flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0.20-0.25) gave **32c**/**34c** (123 mg, 96 %). Diastereoselective crystallization from *n*-hexane afforded pure syn-**34c** (purity by CapGC 99.9 %). M.p. 124-126.5 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.28 (d, J=6.3 Hz, 3H, C_{12}-Me), 1.38 (s, 3H, C_9-Me), 1.53 (s, 3H, C_9-Me), 1.70 (br s, 2H, H_{13}), 1.84-2.13 (m, 1H, H_{11}), 2.36-2.73 (m, 2H, H_{11}, H_{12}), 3.20-3.42 (m, 2H, H_2, H_5), 6.16 (dd, J=5.4 Hz, J=3.0 Hz, 1H, H_3 or H_4), 6.43 (dd, J=5.4 Hz, J=2.7 Hz, 1H, H_3 or H_4); IR (KBr): ν 2965, 1755 (C=O, lactone), 1726 (C=O, ketone), 1385, 1250 cm^{-1}; EI/MS: m/e 246 (M^+), 231 (M-CH_3), 204, 181 (M-$C_5H_5^+$), 66 (C_5H_6); Found 246.1251. $C_{15}H_{18}O_3$ requires 246.1256; Found C, 73.76; H, 7.43. $C_{15}H_{18}O_3$ requires C, 73.15; H, 7.37. Scaling up this reaction also gave satisfactory results, *e.g.* 613 mg (2.67 mmol) **7i** gave 520 mg (79 %) NMR-pure **32c**/**34c**.

11-*{*12-*(*7,10-*Dioxo*-anti-9-*phenyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*enyl)}*-7,10-*dioxo*-syn-12-*methyl*-anti-9-*phenyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **36**

Scaling up the procedure for the synthesis of **34b** using Mg (100 mg, 4.11 mmol), CuCl (40 mg, 0.40 mmol), MeI (320 mg, 2.26 mmol) and **7b** (150 mg, 0.54 mmol) gave a mixture of **34b** and **36**. Dimer **36** was isolated by flash chromatography (silica gel, *n*-hexane /EtOAc = 3/1, Rf = 0.15). M.p. 262-263 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 0.89-2.27 (m, 11H, $H_{11'}$, H_{12}, $H_{12'}$, H_{13}, $H_{13'}$, incl. δ 1.27 (d, J=6.4 Hz, 3H, C_{12}-Me)), 2.56 (dd, J=12.0 Hz, J=8.2 Hz, 1H, $H_{11'}$), 3.16-3.29 (m, 1H, $H_{2'}$ or $H_{5'}$), 3.33-3.53 (m, 3H, H_2, H_5, $H_{2'}$ or $H_{5'}$), 5.27 (s, 1H, H_9 or $H_{9'}$), 5.38 (s, 1H, H_9 or $H_{9'}$), 5.47 (dd, J=5.6 Hz, J=2.8 Hz, 1H), 6.07 (dd, J=5.6 Hz, J=2.8 Hz, 1H), 6.31 (dd, J=5.6 Hz, J=2.8 Hz, 1H), 6.56 (dd, J=5.6 Hz, J=2.8 Hz, 1H, H_3, H_4, $H_{3'}$, $H_{4'}$), 7.02-7.49 (m, 10H, 2xPh); IR (KBr): ν 2970, 1760 (C=O, lactone), 1742 (C=O), 1450, 1112, 702 cm^{-1}; EI/MS: m/e 572 (M^+), 528 (M-CO_2),

506 (M-C_5H_6), 281 ($C_{18}H_{16}O_3$+1), 214 ($C_{18}H_{16}O_3$-C_5H_6), 105 ($C_6H_5CO^+$), 66 (C_5H_6); Found 572.220. $C_{37}H_{32}O_6$ requires 572.220.

7,10-*Dioxo*-anti-11,12-*epoxy*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*tridec*-3-*ene* **37a**

To a vigorously stirred soln of **7a** (60 mg, 0.297 mmol) in CH_2Cl_2/MeOH (4/4 ml) was added: H_2O_2 (0.35 g 40 % aq, 4.12 mmol) and NaOH (1.5 ml 0.2 N, 0.3 mmol). The resulting mixture was stirred for another 20 min at r.t., extracted with $CHCl_3$ (3x), washed (H_2O, 2x), dried ($MgSO_4$) and concentrated *in vacuo*, to give NMR-pure **37a** (49 mg, 76 %) as a white solid. M.p. dec.>205 °C with concomitant sublimation > 130 °C (after recrystallization from *n*-hexane /EtOAc = 1/3); ^{1}H-NMR: δ 1.74 A of AB (dt, ^{2}J=10.4 Hz, J=1.6 Hz, 1H, H_{13}), 1.86 B of AB (dt, ^{2}J=10.4 Hz, J=2.0 Hz, 1H, H_{13}), 3.26 (br s, 1H, H_2 or H_5), 3.40-3.51 (m, 2H, H_2 or H_5 and H_{12}), 3.88 (d, J=2.0 Hz, 1H, H_{11}), 4.06 A of AB (d, ^{2}J=10.0 Hz, 1H, H_9), 4.26 B of AB (d, ^{2}J=10.0 Hz, 1H, H_9), 6.19 (dd, $^3J_{cis}$=5.6 Hz, ^{4}J=3.0 Hz, 1H, H_3 or H_4), 6.35 (dd, $^3J_{cis}$=5.6 Hz, ^{4}J=3.0 Hz, 1H, H_3 or H_4); IR (KBr): ν 2980, 1750 (C=O, lactone), 1380, 1220, 1040 cm^{-1}; EI/MS: m/e 218 (M^+), 66 (C_5H_6); Found C, 66.16; H, 4.57. $C_{12}H_{10}O_4$ requires C, 66.05; H, 4.62.

7,10-*Dioxo*-anti-11,12-*epoxy*-9-anti-*phenyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*tridec*-3-*ene* **37b**

The same procedure as described for the preparation of **37a** was applied, using **7b** (1.43 g, 5.14 mmol), MeOH (28 ml), CH_2Cl_2 (28 ml), H_2O_2 (7.0 ml 35 % aq, 0.072 mol) and NaOH (8.4 ml 0.2 N, 1.68 mmol) to afford NMR-pure **37b** (1.50 g, 99 %) as a white solid. M.p. 176-182 °C with concomitant sublimation > 130 °C (after recrystallization from MeOH or EtOAc /*n*-hexane = 1/3). ^{1}H-NMR: δ 1.94 (t, J=1.5 Hz, 2H, H_{13}), 3.22 (d, J=2.1 Hz, 1H, H_{12}), 3.40-3.60 (m, 2H, H_2, H_5), 3.88 (d, J=2.1 Hz, 1H, H_{11}), 5.20 (s, 1H, H_9), 6.11 (ddd, $^3J_{cis}$=5.7 Hz, J=4.0 Hz, J=0.9 Hz, 1H, H_3 or H_4), 6.31 (ddd, $^3J_{cis}$=5.7 Hz, J=4.0 Hz, J=0.6 Hz, 1H, H_3 or H_4), 7.36 (s, 5H, C_9-Ph); ^{13}C-NMR: δ 47.1 (d), 47.9 (t, C_{13}), 51.5 (d, C_2, C_5), 57.6 (d), 59.7 (d, C_{11}, C_{12}), 65.0 (s), 67.1 (s, C_1, C_6), 85.1 (d, C_9), 126.2 (d), 128.0 (d), 128.6 (d), 134.7 (s), 135.1 (d), 136.3 (d, C_3, C_4, Ph), 174.6 (s, C_7), 203.0 (s, C_{10}); IR (KBr): ν 2960, 1775 (C=O, lactone), 1746 (C=O, ketone), 1250, 1212, 1190 cm^{-1}; EI/MS: m/e 294 (M^+), 228 (M-C_5H_6), 160 (M-C_6H_5CHO-CO), 132, 105, 77, 66 (C_5H_6); Found 294.0894. $C_{18}H_{14}O_4$ requires 294.0892.

7,10-*Dioxo*-anti-11,12-*epoxy*-9-syn-t-*butyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*tridec*-3-*ene* **37c**

The same procedure as described for the preparation of **37a** was applied, using **7c** (0.19 g, 0.736 mmol), MeOH (4 ml), CH_2Cl_2 (4 ml), H_2O_2 (1.0 ml 35 % aq, 10.3 mmol) and NaOH (1.2 ml 0.2 N, 0.24 mmol) to yield NMR-pure **37c** (0.202 g, 100 %) as a white solid. M.p. 164-165 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1 08 (s, 9H, C_9-*t*-Bu), 1.71 A of AB (dt, $^2J_{AB}$=9.9 Hz, J=1.8 Hz, 1H, H_{13}), 1.87 B of AB (d, J_{AB}=9.9 Hz, 1H, H_{13}), 3.38-3.48 (m, 2H, H_2 or H_5 and H_{12}), 3.65 (br s, 1H, H_2 or H_5), 3.92 (d, J=2.1 Hz, 1H, H_{11}), 4.03 (s, 1H, H_9), 6.12 (dd, $^3J_{cis}$=5.4 Hz, J=3.0 Hz, 1H, H_3 or H_4), 6.30 (dd, $^3J_{cis}$=5.4 Hz, J=3.0 Hz, 1H, H_3 or H_4); IR (KBr): ν 3070, 2970, 1765 (C=O,

lactone), 1740 (C=O, ketone), 1230, 1030 cm^{-1}; EI/MS: m/e 275 (M^++1), 257 (M+1-H_2O), 237, 219, 209 (M+1-C_5H_6), 161; Found C, 70.40; H, 6.53. $C_{16}H_{18}O_4$ requires C, 70.06; H, 6.61.

7,10-*Dioxo*-anti-11,12-*epoxy*-9-syn-n-*hexyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*tridec*-3-*ene* **37d**

The same procedure as described for the preparation of **37a** was applied, using **7d** (0.122 g, 0.427 mmol), MeOH (3.5 ml), CH_2Cl_2 (3.5 ml), H_2O_2 (1.0 ml 35 % aq, 10.3 mmol) and NaOH (1.0 ml 0.2 N, 0.2 mmol) to give NMR-pure **37d** (0.118 g, 92 %) as a white solid. M.p. 98-100 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 0.73-1.71 (m, 13H, C_9-$(CH_2)_5CH_3$), 1.79 (s, 2H, H_{13}), 3.22 (br s, 1H, H_2 or H_5), 3.36-3.47 (m, 2H, H_2 or H_5 and H_{12}), 3.86 (d, J=2.0 Hz, H_{11}), 4.00-4.20 (m, 1H, H_9), 6.14 (dd, $^3J_{cis}$=5.6 Hz, J=2.8 Hz, 1H, H_3 or H_4), 6.29 (dd, $^3J_{cis}$=5.6 Hz, J=2.8 Hz, 1H, H_3 or H_4); IR (KBr): ν 1757 (C=O, lactone), 1738 (C=O, ketone), 1220, 1190 cm^{-1}; EI/MS: m/e 302 (M^+), 237 (M-$C_5H_5^+$), 189, 66 (C_5H_6); Found C, 71.02; H, 7.43. $C_{18}H_{22}O_4$ requires C, 71.50; H, 7.33.

7,10-*Dioxo*-anti-11,12-*epoxy*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*tridec*-3-*en*-9-*spirocyclohexane* **37e**

The same procedure as described for the preparation of **37a** was applied, using **7j** (0.122 g, 0.452 mmol), MeOH (2 ml), CH_2Cl_2 (2 ml), H_2O_2 (0.5 ml 35 % aq, 5.2 mmol) and NaOH (0.6 ml 0.2 N, 0.12 mmol) to yield NMR-pure **37e** (0.103 g, 80 %) as a white solid. M.p. dec.>150 °C with concomitant sublimation > 120 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.20-2.21 (m, 12H, C_9-C(CH_2)$_5$, H_{13}), 3.29-3.47 (m, 3H, H_2, H_5, H_{12}), 3.87 (d, J=2.3 Hz, 1H, H_{11}), 6.05-6.18 (m, 1H, H_3 or H_4), 6.27-6.42 (m, 1H, H_3 or H_4); IR (KBr): ν 2940, 1757 (C=O, lactone), 1736 (C=O, ketone), 1280, 1235, 1195 cm^{-1}; EI/MS: m/e 286 (M^+), 221, 220 (M-C_5H_6), 66 (C_5H_6); Found C, 70.80; H, 6.34. $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34.

7,10-*Dioxo*-9,9-*dimethyl*-anti-11,12-*epoxy*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*tridec*-3-*ene* **37f**

The same procedure as described for the preparation of **37a** was applied, using **7i** (0.45 g, 1.956 mmol), MeOH (13 ml), CH_2Cl_2 (13 ml), H_2O_2 (4.1 ml 35 % aq, 42.2 mmol) and NaOH (4.8 ml 0.2 N, 0.96 mmol) to yield NMR-pure **37f** (0.453 g, 94 %) as a white solid after flash chromatography (silica gel, EtOAc /*n*-hexane = 1/2). M.p. 162-164 °C with concomitant sublimation > 130 °C (after recrystallization from *n*-hexane /CH_2Cl_2 = 10/1). ^{1}H-NMR: δ 1.45 (s, 3H, C_9-Me), 1.50 (s, 3H, C_9-Me), 1.82 (t, J=1.5 Hz, 2H, H_{13}), 3.33-3.43 (m, 3H, H_2, H_5, H_{12}), 3.87 (d, J=2.3 Hz, 1H, H_{11}), 6.14 (ddd, $^3J_{cis}$=5.4 Hz, J=3.0 Hz, J=0.9 Hz, 1H, H_3 or H_4), 6.35 (dd, $^3J_{cis}$=5.4 Hz, J=3.0 Hz, 1H, H_3 or H_4); IR (KBr): ν 2990, 1748 (C=O, lactone), 1393, 1285 cm^{-1}; EI/MS: m/e 246 (M^+), 231 (M-Me), 213 (M-Me-H_2O), 66 (C_5H_6); Found 246.0898. $C_{14}H_{14}O_4$ requires 246.0892.

(-)-(1R,2S,3R,4S,5R,7S,8S,11R,12S)-6,10-*Dioxo*-anti-8-*phenyl*-9-*oxahexacyclo*[6.5.0.$0^{2,5}$.$0^{3,12}$.$0^{4,11}$.-$0^{7,11}$]*tridecane* **40**

A soln of (-)-**7b** (438 mg, 1.576 mmol, $[\alpha]_D^{25}$= -11.3° (c = 1.2; $CHCl_3$), ee 85 % (*Cf.* Chapter 5) in toluene (100 ml) was irradiated for 3 h using a high-pressure mercury arc and a Pyrex filter. After con-

centration *in vacuo* and subsequent flash chromatography (silica gel, EtOAc /*n* hexane = 1/1, I_2) **40** (401 mg, 92 %, $[\alpha]_D^{25}$= - 35 3° (c = 0 57, $CHCl_3$)) was obtained as a pure white solid M p 150 153 °C (after recrystallization from EtOAc /*n* hexane = 1/3) ^{1}H-NMR δ 1 87 A of AB (br d, J_{AB}=12 5 Hz, 1H, H_{13}), 2 27 B of AB (br d, J_{AB}=12 5 Hz, 1H, H_{13}), 2 60 2 78 (m, 1H), 2 84-3 29 (m, 4H, H_1, H_2, H_3, H_4, H_{12}), 3 69 (m, 1H, H_5), 5 49 (s, 1H, H_8), 7 37 (s, 5H, C_8-Ph), ^{13}C-NMR (200 MHz) δ 34 1 (d), 37 5 (d), 39 7 (t, C_{13}), 40 6 (d), 41 9 (d), 44 4 (d), 50 0 (d, C_1, C_2, C_3, C_4, C_5, C_{12}), 58 5 (s), 61 4 (s, C_7, C_{11}), 78 2 (d, C_8), 125 0 (d), 127 9 (d), 134 7 (s, Ph), 173 9 (s, C_{10}), 208 7 (s, C_6), IR (KBr) ν 2980, 1770 (C=O, lactone), 1755 (C=O, ketone), 1450, 1187, 993 cm^{-1}, EI/MS m/e 278 (M^+), 212, 144 (M C_6H_5CHO-CO), 105, 91, 77, Found C, 78 16, H, 5 21 $C_{18}H_{14}O_3$ requires C, 77 68, H, 5 07

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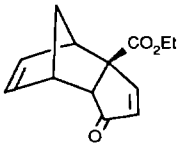
CHAPTER 4

SYNTHESIS OF LACTONE ANNELATED CYCLOPENTENONES FROM BRIDGED [4.3.3]OXAPROPELLANES USING FLASH VACUUM THERMOLYSIS; TOTAL SYNTHESIS OF (±)-SARKOMYCINS

4 1 INTRODUCTION

In the preceding Chapters, it was demonstrated that tricyclodecadienone ester **1** is readily deprotonated by lithium diisopropylamide to give enolate **2**, which can be either alkylated[1] (Chapter 2) or condensed[2] with aldehydes and ketones (Chapter 3) In the latter case, the interesting bridged [4 3 3]oxapropellanes **3** are obtained in good to excellent yields When sterically demanding aldehydes such as benzaldehyde and pivalaldehyde are used as the electrophiles, this formation of lactones **3** also proceeds with a high degree of stereoselectivity Remarkably, in spite of their rather compact structure, tetracyclic lactones **3** possess an increased reactivity toward nucleophilic addition reactions when compared with ester **1** Both hydride reduction and the addition of Grignard or alkyllithium reagents proceed smoothly to give a stereoselective formation of the corresponding 1,4-addition products **4** in excellent yields[2]



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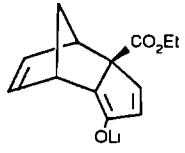

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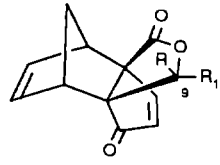

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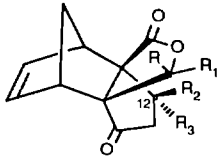

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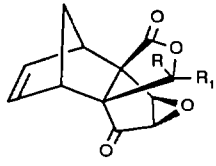

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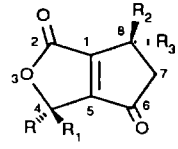


6

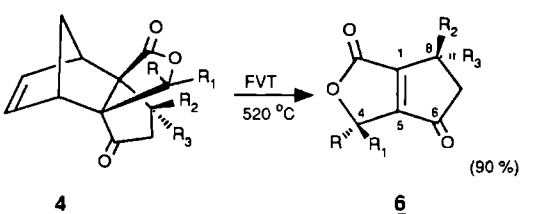
Due to complete shielding of the ketone group in **3** by the substituents at C_9 in the lactone ring, 1,2-addition was not observed at all, even not for reactive species such as MeLi and $LiAlH_4$ Notably, with these reagents no reaction was observed with the lactone moiety in **3** either Nucleophilic epoxidation of **3** afforded in a stereoselective fashion the epoxides **5** in high yields Having attained an efficient and stereoselective route to lactones **4**, it is of interest to establish whether these tetracyclic lactones will undergo a thermal cycloreversion to the interesting lactone annelated cyclopentenones **6** These butenolides **6** then would provide access to sarkomycins because reduction of their central double bond would produce cyclosarkomycins, which have been reported[3] to be excellent precursors for these natural products In this Chapter the successful synthesis of bicyclic lactones **6** from **4**, utilizing

the flash vacuum thermolysis technique, will be described Also the synthetic potential of these compounds for the synthesis of some sarkomycins will be demonstrated

4 2 THE THERMAL CYCLOREVERSION OF BRIDGED [4 3 3]OXAPROPELLANES

The thermal cycloreversion of oxapropellanes **4** was studied in the gas phase, applying the flash vacuum thermolysis technique as described in the appendix of Chapter 2 At a temperature of 520 °C and a pressure of 10^{-2} torr, a smooth and clean [4+2] cycloreversion was observed for all tetracyclic lactones **4**, affording lactone annelated cyclopentenoids **6** in excellent yields (>90 %), with a high degree of purity (Scheme 1) Compounds **6** are unique structures as they contain both a butenolide[4] and a cyclopentenone ring moiety with the double bond as their common structural unit With the exception of **6e** and **6f**, all compounds **6** are crystalline materials This novel class of lactone annelated cyclopentenoids was fully characterized by their spectral data (^{1}H-NMR, ^{13}C-NMR, IR, UV and Mass Spectrometry) Their ^{13}C-NMR spectra (Broad Band and Off Resonance) typically show three singlets at δ 160-170 ppm which must be ascribed to C_2 and the electron-poor olefinic carbon atoms C_1 and C_5, and a singlet at δ 198 ppm originating from the cyclopentenoid C_6-carbonyl atom Their IR spectra showed two strong characteristic absorptions in the carbonyl region at 1755-1765 cm^{-1} for the lactone and 1715 cm^{-1} for the cyclopentenone moiety, respectively Typically, compounds **6** exhibit absorption maxima in their UV spectra at 237 nm

Scheme 1



4 **6**

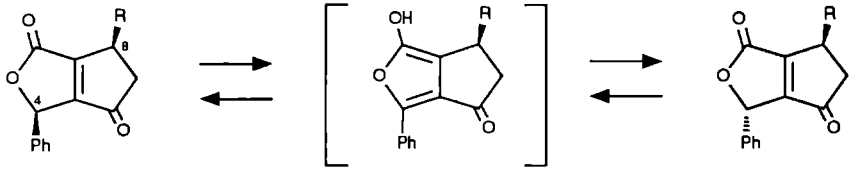
	R	R_1	R_2	R_3		R	R_1	R_2	R_3
e	H	H	H	H	**f**	H	Ph	n Bu	H
b	H	Ph	H	H	**g**	H	Ph	H	Me
c	n hexyl	H	H	H	**h**	Me	Me	Me	H
d	Me	Me	H	H	**i**	Me	Me	H	Me
e	H	Ph	Me	H	**j**	Me	Me	n Bu	H

Although the lactones **6** were generally obtained as pure compounds after recrystallization, in the case of **6e** a chromatographic purification step was needed to obtain an analytically pure sample Surprisingly, TLC analysis of NMR-pure **6e** on silica gave two distinct spots Furthermore, flash chromatographic purification of **6e** on silica led to a mixture of two lactones in a 4 1 ratio Their ^{1}H-NMR spectra revealed that these lactones are epimers, *viz* **6e** and **6g** Although the ^{1}H-NMR spectra of **6e** and **6g** are almost identical, the *cis*- and *trans* structure can readily be distinguished by the $^5J_{H4\,H8}$ bishomoallylic coupling constants which amount to 3 0 and 1 6 Hz, respectively Apparently, epimerization of **6e** at one of the chiral centers, C_4 or C_8, had occurred during this chromatographic purification step This conversion of **6e** into **6g** presumably proceeds *via* an acid catalyzed enolization to the relatively stable 2-hydroxyfuran derivative[5] **7** (Scheme 2) The occurrence of such an epimerization during the thermal cycloreversion of either **4e** or **4g** was excluded, because the crude pro-

ducts **6e** and **6g** obtained by the respective thermolyses, did not contain any of the other epimer as was shown by ^{1}H-NMR and ^{13}C-NMR analyses

Similar results were obtained for butenolide **6f** Flash vacuum thermolysis of **4f** produced **6f** exclusively However, on silica gel epimerization took place to give a mixture of **6f** and **6k** in a molar ratio of approximately 3 1 (Scheme 2)

Scheme 2



6e R=Me
6f R=n Bu

7

6g R=Me
6k R=n-Bu

Capillary GC analysis of pure **6e** and **6g** both gave the same two distinct peaks of approximately equal height This observation points to an epimerization of **6e** and **6g** during Capillary GC As a merely thermal epimerization of these 4-phenyl butenolides is unlikely to occur[6], these interconversions are best rationalized by an acid catalyzed epimerization in the chromosorb pre-filter of the Capillary GC apparatus

It should be noted that the epimerization of lactones **6e**, **6f** and **6g** on silica gel in principle also can be explained by invoking a ring opening and ring closure process involving an alkyl ester type cleavage of the lactone ring Although this process cannot be ruled out, it seems unlikely because it would require the intermediacy of a highly unstable vinologous α-keto carbocation Moreover, no such epimerizations at the γ-carbon atom have been reported for similarly substituted saturated γ-lactones, whereas there is precedent for such acid catalyzed epimerizations at the C_5 position in γ-butenolides[5]

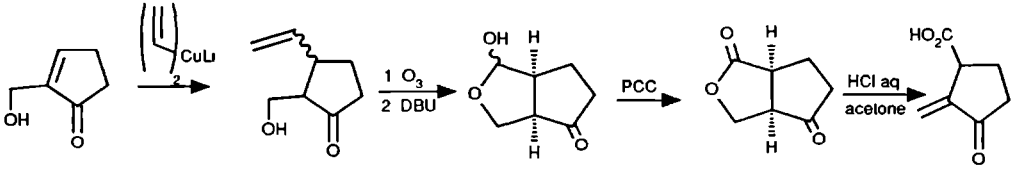
The thermal cycloreversion of bridged [4 3 3]oxapropellanes is an efficient, general and stereoselective route to the hitherto unknown class of lactone annelated cyclopentenones **6**, starting from readily availabe ester **1** As this ester **1** is available as optically pure antipodes, this route also constitutes, in principle, an enantioselective synthesis of **6** (see Chapter 5)

In the following Sections some chemical features of these novel bicyclic cyclopentenoids **6** will be uncovered

4.3 REGIO AND STEREOSELECTIVE REDUCTION OF LACTONE ANNELATED CYCLOPENTENOIDS

The labile sarkomycin[7] **12** has been the subject of previous synthetic studies[3,8] because of its antitumor[9] and antiviral[10] activity. Several of the regioselective routes[3,11,12] to sarkomycin **12** involve the intermediacy of lactone annelated cyclopentanone **11a** (Scheme 3). Marx and Minaskanian[3] prepared cyclosarkomycin **11a** in five steps, starting from 2-methoxycarbonylcyclopent-2-enone. Smith *et al*[11] obtained lactone **11a** in three steps in an overall yield of 73 %. Their route starts from α-(hydroxymethyl)cyclopentenone **8** which on reaction with lithiumdivinyl cuprate gave unsaturated keto alcohol **9** as an epimeric mixture. Subsequent ozonolysis afforded lactol **10** which was oxidized into cyclosarkomycin **11a**. Careful acid-catalyzed retrolactonization[3] of **11a**, followed by dehydration, then leads to sarkomycin in a yield of 30-40 %.

Scheme 3



8 **9** **10** **11a** **12**

An alternative synthesis of lactone **11a** would involve reduction of the central double bond in lactone annelated cyclopentenone **6a**. If successful, a new total synthesis of the natural product sarkomycin **12**, starting from tricyclic ester **1**, would be feasible. As a wide range of bicyclic cyclopentenoids **6** is accessible, selective reduction of their central double bond, followed by retrolactonization constitutes a conceivable route to various sarkomycin analogues.

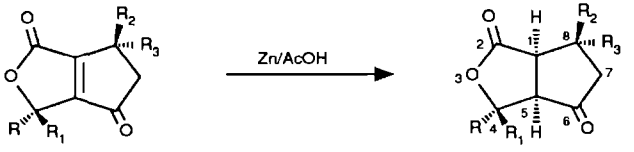
Several methods for the reduction of the C_1-C_5 double bond in **6** were considered. Catalytic hydrogenation, which was expected to take place selectively at the olefinic bond, was attempted in ethanol with Pd/C as the catalyst. However, the results were unsatisfactory for **6b** and **6d**, contrasting to smooth hydrogenation of the structurally related ethyl cyclopent-1-en-3-one carboxylate[13] under identical conditions. On the other hand the reluctance of **6b** and **6d** to undergo hydrogenation is in agreement with the general finding that double bonds common to two rings are most difficult to hydrogenate[14].

A possible alternative for this reduction is the use of zinc in acetic acid. An effective chemoselective reduction of unsaturated ketones, in which the double bond is located between two carbonyl functions, to the corresponding saturated 1,4-diketones using this reducing agent has been described in several reports[15]. Gratifyingly, the desired chemoselective reduction of compounds **6** to **11** was observed for all cyclopentenones **6** under relatively mild conditions. The explanation for the efficacy of this reaction probably lies in the energy relief accompanying the reduction process of the strained double

bond. By carefully optimizing the reaction temperature for each substrate **6** during each reaction cyclosarkomycins **11** could be prepared in reasonable to good overall yields (Scheme 4). The reaction temperature had to be kept as low as possible to avoid the uncontrolled ring opening[16] of **11** to sarkomycins *(vide infra).*

The reduction of the central double bond in **6** leads in all cases to the formation of two new chiral centers, *viz.* at C_1 and C_5 in **11**. Consequently, mixtures of at least two diastereomers **11** may, in principle at least, be obtained by reducting **6** with zinc in acetic acid. The lactone and the cyclopentanone rings may be either *trans* or *cis*-fused. The zinc reduction of enones and enediones generally affords the thermodynamically most stable product. Therefore a stereospecific *cis*-reduction of the central double bond in **6** may be expected because of the considerably higher potential energy of the *trans*-fused 3-oxabicyclo[3.3.0]octane system as compared with the *cis*-fused analogue. Indeed, the zinc reduction proceeded stereospecifically for all substrates **6** studied, to afford exclusively the *cis*-fused lactone annelated cyclopentanones **11**.

Scheme 4



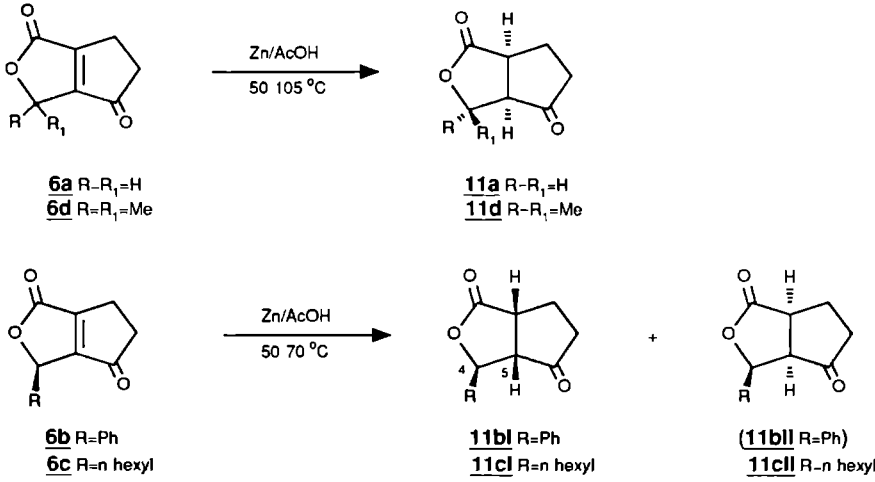
6 **11**

Accordingly, the Zn/AcOH reduction of **6a** and **6d**, which are prochiral, diastereospecifically afforded **11a** and **11d** in 84 and 65 % yield, respectively (Scheme 5). Cyclosarkomycin **11a** prepared in this manner was identical in all respects with that reported by Marx and Minaskanian[3].

The presence of chiral centers in **6** others than C_1 and C_5 may lead to mixtures of diastereomers of **11**. In order to quantify the effect of substitution in **6** on the stereochemistry of this zinc reduction, a series of C_4 and C_8 substituted butenolides **6** was investigated. The zinc reduction of 4-phenyl substituted butenolide **6b** appeared to be stereospecific (Scheme 5). A single compound was obtained in 89 % yield to which, on basis of a detailed ^{1}H-NMR analysis, structure **11bI** was assigned. Especially, the observed value of 2 Hz for the $^3J_{H4,H5}$ coupling in 4-phenyl cyclosarkomycin **11bI** proves the *trans*-relationship between these two protons. For the related C_8-methyl and C_8-*n*-butyl substituted phenyllactones **11eII** and **11fII**, in which the H_4 and H_5 protons mutually possess a *cis*-orientation, a coupling constant of *ca.* 8 Hz was found *(vide infra).* These assignments are in agreement with the results of Feringa *et al*[5] who reported that the *cis* and *trans*-isomers of 4-substituted 5-alkoxybutyrolactones could reliably be distinguished on the basis of a small (J<2 Hz) or no proton coupling for the C_5 hydrogen for the *trans*-isomer and a 5-8 Hz coupling for the *cis*-isomer.

Evidently, the more stable diastereomer **11bI** is the exclusive product in this zinc reduction of **6b**.

Scheme 5



6a R-R$_1$=H
6d R=R$_1$=Me

11a R-R$_1$=H
11d R-R$_1$=Me

6b R=Ph
6c R=n hexyl

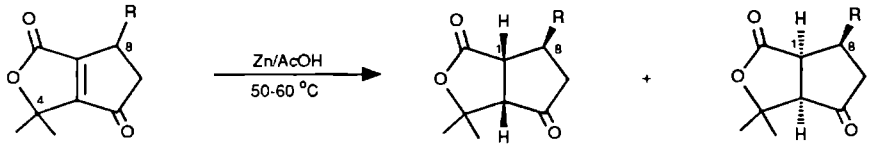
11bI R=Ph
11cI R=n hexyl

(**11bII** R=Ph)
11cII R=n hexyl

No trace of the isomer **11bII** could be detected In contrast to the 4-phenyl substituted butenolide **6b**, reduction of *n*-hexyl analogue **6c** under identical conditions, led to a mixture of diastereomers **11cI** and **11cII** in a ratio of 2 1 The preference for isomer **11cI**, the presumed thermodynamically more stable one because it has the hexyl substituent at the *convex* side of the molecule, is considerably less pronounced than for **11bI** which was obtained as the exclusive product In the case of **6h** and **6j**, which have a substituent at C_8 and a geminal dimethyl group at C_4, a high degree of diastereoselectivity was observed during the reduction with zinc and acetic acid Under standard conditions, 4,4,8-trimethyl butenolide **6h** afforded a mixture of the lactones **11hI** and **11hII** in a ratio of 1 8 with a total yield of 68 % (Scheme 6) For 8 *n* butyl derivative **6j** the reduction appeared to be completely diastereoselective, only **11jII** was obtained according to capillary gas chromatography and ^{13}C-NMR spectroscopy The structures of the products were unequivocally established by ^{1}H NMR spectral data The *cis*-relationship between the lactone moiety and the C_8-alkyl substituents in **11hII** and **11jII** was deduced from the ^3J_H coupling constant for protons H_1 and H_8, which amounts to 7-8 Hz For compound **11eI** (Scheme 7), which has a *trans*-relationship between its lactone moiety and the C_8-methyl group, hardly any coupling between H_1 and H_8 is observed Remarkably, the predominant diastereomers **11hII** and **11jII** have the C_8-alkyl group at the *concave* side of the molecule, which is, as evident from a study of molecular models, the thermodynamically less stable one This stereochemical result is opposite to that observed for **6b** and **6c** where the predominant product has the C_4 substituent at the *convex* side of the molecule

In order to quantify the effect of monosubstitution at both C_4 and C_8 on the stereochemical course of the zinc reduction, the 4 phenyl 8-alkyl substituted derivatives **6e**, **6f** and **6g** were investigated (Scheme 7) For the *cis*-8-methyl-4-phenyl and 8-*n*-butyl-4-phenyl butenolides **6e** and **6f**, the Zn/AcOH reduction in both cases gave mixtures of three products in good overall yields (69-85 %)

Scheme 6



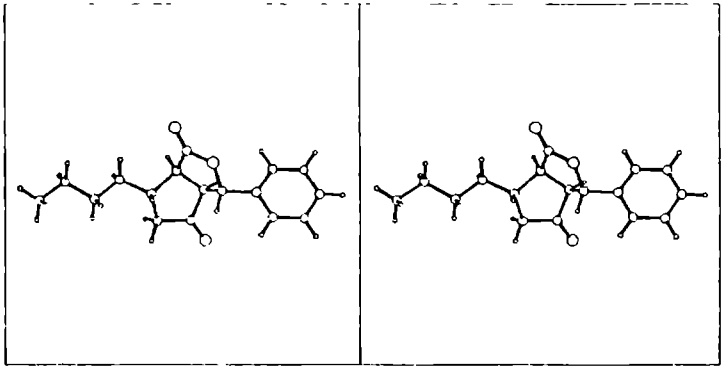
6h R=Me
6j R=n-Bu

11hI R=Me

11hII R=Me
11jII R= n-Bu

Reduction of **6e** led to the formation of lactones **11eI**, **11g** and **11eII** in a ratio of 6:2:1, whereas **6f** similarly afforded **11fI**, **11k** and **11fII** in a ratio of 9:3:4. ^{1}H-NMR analysis and for **11fI** an X-ray diffraction analysis[17] (Fig. 1), established the correct structures for all these compounds.

Fig. 1

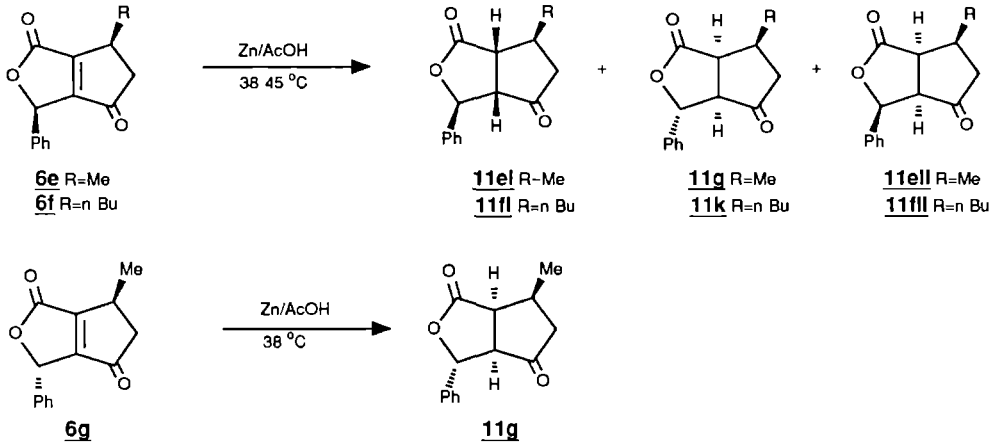


The formation of the *trans*-substituted 4-phenyl-8-alkyl lactones **11g** and **11k** can readily be explained by assuming that part of the starting butenolides **6e** and **6f** undergo an acid-catalyzed epimerization at either C_4 or C_8 to form the thermodynamically more stable *trans*-isomers **6g** and **6k** prior to the actual reduction. As has been described above such an epimerization of lactones **6** does take place under acidic conditions. Epimerization during or after the reduction process seems unlikely as it would require an epimerization at the non-activated C_8 carbon atom (no adjacent carbonyl group) of **11eI** or **11fI**, respectively.

The predominant product of the reduction of **6e** and **6f**, *viz.* **11eI** and **11fI**, respectively, have both substituents at the *convex* side of the molecule. Molecular models clearly suggest that these compounds are thermodynamically more stable than **11eII** and **11fII**, respectively, having both substituents at the *concave* side. Reduction of **6g** produced only one diastereomer, *viz.* **11g** in a yield of 75 %, which has the C_4-phenyl group at the *convex* side and the C_8-methyl group at the *concave* side.

The zinc/acetic acid reduction of the butenolides **6** can satisfactorily be explained by invoking the classical mechanism[18] for these metal reductions (Scheme 8). Initial electron transfer from zinc to the C_6-ketone function gives radical anion **13**, which on a second electron transfer from the metal is

Scheme 7



6e R=Me
6f R=n Bu

11el R-Me
11fl R=n Bu

11g R=Me
11k R=n Bu

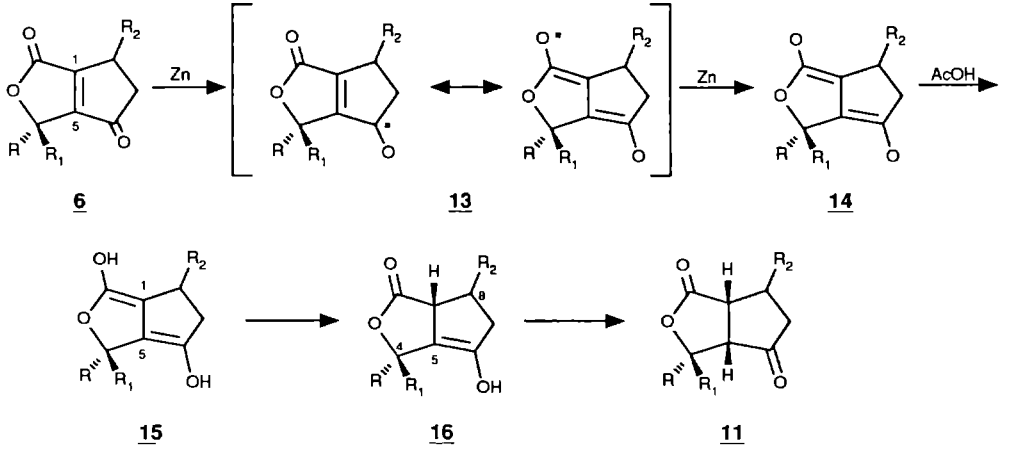
11ell R=Me
11fll R=n Bu

6g

11g

transformed in dienediolate **14** Subsequent protonation by acetic acid then leads to dienediol **15** The order of electron transfer and protonation shown in Scheme 8 may be slightly different, in any case dienediol **15** is considered as an essential intermediate The planar double enol **15** undergoes ketonization in two consecutive steps, the first one being the formation of the lactone group, the second one the C_6-ketone function The order of the ketonization steps is dictated by the differences in pk_a (*ca* 26 for the lactone and *ca* 22 for the ketone[19]) As far as the stereochemistry of these two steps is concer-

Scheme 8



6 13 14

15 16 11

ned, once the proton transfer to C_1 has started from one face of the dienediol, that to C_5 then must occur from the same side in order to produce *cis*-fused cyclosarkomycins **11** This explains the formation of **11a** from **6a** and of **11d** from **6d** It is of importance to note that the reduction is a kinetically controlled process, no product equilibration has been observed in any case Apart from that, product

interconversion, *e.g.* **11hI** into **11hII** and vice versa, would require concurrent epimerization at C_1 and C_5, which is considered highly unlikely.

The diastereoselective formation of **11bI** from **6b** can be understood by invoking a kinetic preference for the thermodynamically more stable isomer. The initial proton transfer to C_1 (conversion of **15** into **16**) apparently experiences no steric hindrance from the substituent at the remote C_4-atom. The kinetic preference for **11cI** is less pronounced, because a considerable amount of diastereomer **11cII** is also obtained. Inspection of molecular models suggests that the steric congestion caused by the hexyl substituent in **11cII** can partly be accommodated by the flexibility of the cyclosarkomycin skeleton. A phenyl group at C_4 in **11bII** is in this respect much more sterically demanding.

Interesting substrates are **6h** and **6j**, which have a substituent at C_8 adjacent to the site of the initial protonation (conversion of **15** into **16**). The experimental results indicate that initial protonation is now being governed by the sterically demanding substituents at C_8. Protonation at C_1 *anti* to the substituent at C_8 leads to the predominant products **11hII** and **11jII**, respectively, despite the fact that these products have the C_8-alkyl substituent at the thermodynamically less favorable *concave* side of the molecule.

In the substrates **6e** and **6f** the kinetic preference is determined by two opposing effects, *viz.* the thermodynamic stability of the products (the C_4- and C_8-substituents both at the *convex* side is favorable in this respect) and C_1-protonation *anti* to the C_8-alkyl substituent in going from **15** to **16**. The experimental results reveal that the former prevails (ratio **11eI**:**11eII** = 6:1; **11fI**:**11fII** = 9:4). In substrate **6g** both effects, the thermodynamic product stability and the *anti*-protonation of C_1 work in the same direction, resulting in the exclusive formation of **11g** (the phenyl group at C_4 is on the *convex* side, while the proton at C_1 is positioned *anti* to the C_8-CH_3 group).

In conclusion, the zinc/acetic acid reduction of the annelated butenolides **6** is an effective method with a high degree of stereocontrol, the outcome of which is strongly determined by the substituents at C_4 and/or C_8. The resulting bicyclic lactones **11** are of interest for the preparation of sarkomycin analogues.

4.4 DIRECT SYNTHESIS OF SARKOMYCIN ANALOGUES BY ZINC REDUCTION OF LACTONE ANNELATED CYCLOPENTENOIDS

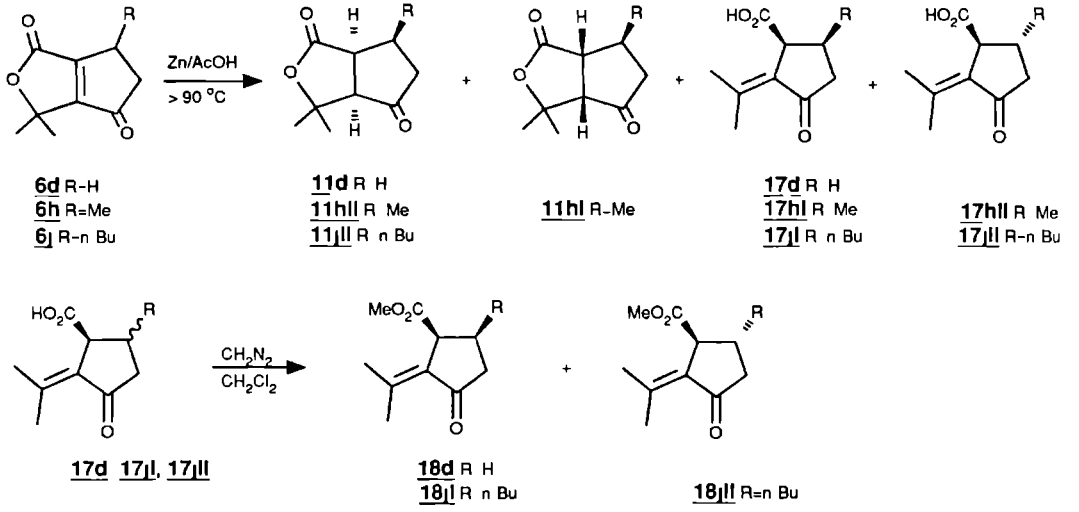
In order to find optimum conditions for the reduction of 4,4-dimethyl butenolide **6d** with zinc in acetic acid, the reaction temperature was varied. At temperatures higher than 60 °C, not only the formation of lactone **11d** was observed, but also a considerable amount of sarkomycin analogue **17d** was obtained (Scheme 9). This fortuitous finding initiated a more detailed analysis of the possibility of a direct synthesis of sarkomycin analogues from butenolides **6**.

At an optimum temperature of 90 °C, dimethyl sarkomycin **17d** was isolated as a white crystalline compound in a relatively good yield of 62 %, together with 37 % of cyclosarkomycin **11d**. Both compounds could simply be separated by acid-base extraction. Sarkomycin **17d** was characterized by its

^{1}H-NMR spectrum which typically shows two singlets at δ 1 96 and 2 27 ppm for the vinylic methyl groups, and a doublet at δ 3 84 ppm for proton H_3 Its IR spectrum revealed the anticipated strong ab sorptions in the carbonyl region at 1740 cm^{-1} for the carboxylic function and at 1715 cm^{-1} for the cyclopentenone ring

Under the same conditions, the zinc reduction of C_8 substituted dimethyl butenolides **6h** and **6j** also gave mixtures of cyclosarkomycins and sarkomycins Disappointingly, the sarkomycin analogues were only obtained in rather poor yields The zinc reduction of **6h** in acetic acid afforded a diastereo meric mixture of sarkomycins **17hI** and **17hII** in a total yield of 30 %, while **6j** yielded **17jI** and **17jII** in 26 % yield only The corresponding methyl esters **18d**, **18jI** and **18jII** were prepared by treating the acids **17d**, **17jI** and **17jII** with diazomethane

Scheme 9



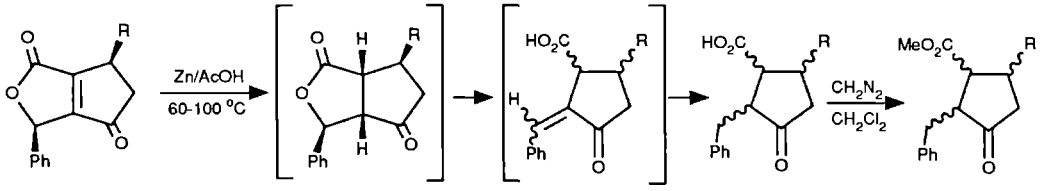
The formation of a diastereomeric mixture of sarkomycins by the reductive retrolactonization of **6** is readily explained by assuming that initially reduction will lead to a diastereomeric mixture of lac tones **11** Under the applied acidic conditions, subsequent eliminative lactone opening takes place to afford the observed products **17** In principle, epimerization at C_1 in **17** is also conceivable for those sarkomycins **17** that have the carboxylic acid function in a *cis*-position with respect to the adjacent C_4 substituent This then will lead to the thermodynamically more stable *trans* compounds **17II**

Attempts to prepare the natural occurring sarkomycin **12** from **6a**, following the above procedure, were not successful No conditions could be found that led to sarkomycin Apparently, the retrolacto-nization of **11** is strongly dependent on its substitution pattern

Illustrative for such a substitution effect is the outcome of the zinc reduction of phenyl substituted butenolides **6b**, **6e** and **6f** (Scheme 10) Under similar conditions as applied above for **6d**, **6h** and **6j** no

sarkomycins were formed at all Instead, a mixture of cyclosarkomycins **11** and dihydrosarkomycins **20b**, **20e** and **20f** was obtained, respectively Acid-base extraction again allowed the isolation of diastereomeric mixtures of **20b**, **20e** and **20f**, respectively in yields varying from 25 % for **20f** to *ca* 70 % for **20b** and **20e** The corresponding methyl esters **21b**, **21e** and **21f** were obtained in almost quantitative yield, by treatment with diazomethane Attempted separation of the respective diastereomers **21b**, **21e** and **21f**, by flash chromatography, failed

Scheme 10



6b R=H
6e R=Me
6f R=n Bu

11

19

20b R=H
20e R=Me
20f R=n Bu

21b R-H
21e R Me
21f R=n Bu

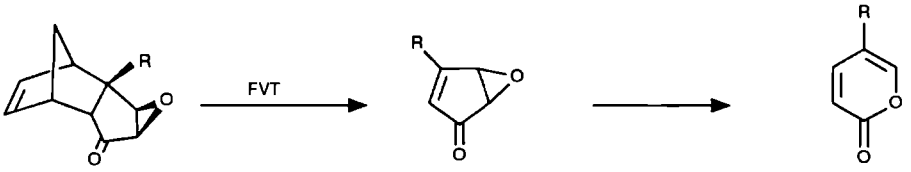
The dihydrosarkomycins **20** are the ultimate products of two successive reductions The initially formed lactones **11** partly undergo a retrolactonization reaction to give the corresponding sarkomycins **19** Under the reductive conditions applied, the phenyl substituted *exo* cyclic enones are apparently not stable, but rapidly undergo reduction of the *exo*-methylene double bond to give the dihydrosarkomycins **20** A facile reduction of a β-phenyl substituted enone moiety has been reported earlier[15] and can be attributed to the lowered reduction potential of such β-substituted enones

Evidently, the direct formation of sarkomycins from the butenolides **6** by a reductive retrolactonization process, using zinc in acetic acid, has only limited value In some cases the intermediate lactone **11** is too stable to give the subsequent retrolactonization reaction at the applied temperatures, in other cases the sarkomycins are readily formed but undergo a subsequent reduction to dihydrosarkomycins (*e g* **20**)

4 5 SYNTHESIS OF LACTONE ANNELATED CYCLOPENTADIENONE OXIDES BY FLASH VACUUM THERMOLYSIS OF OXAPROPELLANE EPOXIDES

In previous reports[20 21] it was shown that the thermolytic conversion of tricyclodecenone epoxides **22**, using the flash vacuum thermolysis technique, strongly depends on the nature of the substituent R (Scheme 11) When the R substituent comes in conjugation with the double bond generated during the thermal cycloreversion reaction, the cyclopentadienone oxides **23** could be isolated[20] When the conjugaton of the generated enone moiety is not extended by a π-system in the R substituent, the epoxides **23** undergo a further rearrangement to 2-pyrones **24** Recently, tricyclodecenone epoxides were used as synthons for the preparation of the mould metabolite (±) terrein[21] (Chapter 1)

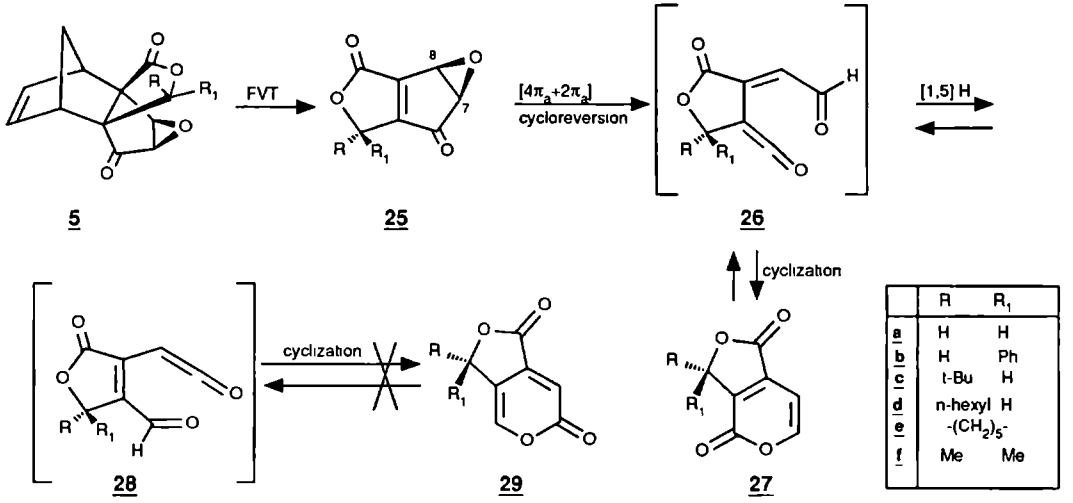
Scheme 11



22 **23** **24**

In Chapter 3 the stereoselective nucleophilic epoxidation of oxa[4.3.3]propellanes **3** into the corresponding oxides **5** was described. This section deals with the thermal conversion of **5** into the desired bicyclic cyclopentadienone oxides **25** using the flash vacuum thermolysis technique. When flash vacuum thermolysis of **5a** and **5c**-**5f** was conducted at *ca.* 450 °C, the desired annelated cyclopentadienone oxides **25** could be detected by ^{1}H-NMR spectroscopy (Scheme 12). These compounds characteristically exhibit two doublets of the epoxy protons H_7 and H_8 (*e.g.* at δ 4.07 and 4.33 ppm for **25f**), with a small coupling constant ($^3J_{H7,H8}$=2.3 Hz). Although these epoxides **25** were not isolated as such, it could be concluded from their ^{1}H-NMR spectra that they were formed in a highly stereoselective way.

Scheme 12



5 **25** **26** **28** **29** **27**

Flash vacuum thermolysis of **5a**-**5f** at a more elevated temperature (*ca.* 525 °C) afforded bicyclic pyrones **27a** and **27c**-**27f** in yields of *ca.* 50 % (Scheme 12). However, the phenyl derivative **5b** showed a deviating thermal behavior. FVT of **5b** yielded a mixture of products, which consisted of some pyrone **27b** and three aldehydes as by-products, as was deduced from the presence of three signals near δ 10 ppm in the ^{1}H-NMR spectrum of the crude reaction mixture. Surprisingly, FVT of *t*-butyl derivative **5c** only gave **27c** in 51 % yield at a temperature of 580 °C. Below this temperature starting material **5c** was mainly recovered. An explanation for this reluctance of **5c** to undergo a retro

Diels-Alder fragmentation presumably is the increase of the Van der Waals energy in the transition state, caused by the sterically demanding *endo-t*-butyl group.

It should be noted that **27** constitutes a pyrone which is annelated with a butenolide. This new class of compounds was characterized by spectroscopic means. Typically, their IR spectra contain two strong absorptions in the carbonyl region, *viz.* at 1780 cm^{-1} (butenolide) and 1745 cm^{-1} (pyrone). Their UV spectra show absorption maxima at 311 nm. In the ^{1}H-NMR spectrum of **27a** its H_5-absorption characteristically appears at low field (δ 7.68 ppm) as a doublet of a doublet ($^3J_{H4,H5}$=5.2 Hz and $^6J_{H5,H9}\cong$0.8 Hz).

The thermal formation of the annelated 2-pyrones **27** from the intermediate cyclopentadienone oxides **25** can be rationalized mechanistically[22] as is depicted in Scheme 12. This mechanism involves a $[4\pi_a+2\pi_a]$-cycloreversion to form ketene aldehyde **26** which equilibrates *via* a sigmatropic [1,5] H-shift with **28**. Subsequently, both **26** and **28** can cyclize to the bicyclic pyrones **27** and **29**, respectively. In all cases studied, the formation of pyrones **29** was not observed. As the formation of both **27** and **29** is thermodynamically controlled, the relative stabilities of **27** and **29** are expected to govern the observed product distribution. Thus, the exclusive formation of **27** in the thermal conversion from **25** may be the result of its somewhat greater stability in comparison with **29**. Structure **29** possesses two unfavorable exo-cyclic double bonds with respect to its butenolide moiety, conversely in **27** these olefinic bonds are in a more favorable endo-cyclic position with respect to both rings.

In conclusion, flash vacuum thermolysis of **5a**-**5f** constitutes a suitable method for the synthesis of bicyclic pyrone derivatives **27**. Although the intermediate bicyclic cyclopentadienone oxides **25** could not be isolated as such, their formation from **5** was elicited by their characteristic ^{1}H-NMR spectral data.

4 6 EXPERIMENTAL PART

General

The remarks given in Section 2 5 also apply here

Syntheses

2,6-*Dioxo*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **6a**

Lactone **4a** (52 mg, 0 255 mmol) was subjected to FVT [sample temp 85-95 °C, oven temp 520 °C, p 1 5 10^{-2} mm Hg, cold trap temp · -196 °C] to give **6a** (30 mg, 85 %) as a NMR-pure white solid M p 107-109 °C (after recrystallization from *n*-hexane /CH_2Cl_2 = 3/1) ^{1}H-NMR δ 2 69-2 93 (m, 2H, H_7, H_8), 2 93-3 13 (m, 2H, H_7, H_8), 5 00 (t, J=3 0 Hz, 2H, H_4), IR (KBr) ν 1760 (C=O, lactone), 1710 (C=O, enone), 1442, 1205, 1055, 995 cm^{-1}, EI/MS m/e 138 (M^+), 110 (M-CO), 82 (M-2CO), 66 (M CO-CO_2), UV (MeOH) λ_{max} 237 nm (14000), Found 138 0321 $C_7H_6O_3$ requires 138 0317 Found C, 60 27, H, 4 39 $C_7H_6O_3$ requires C, 60 87, H, 4 38

2,6 *Dioxo*-4-*phenyl*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **6b**

FVT of **4b** (360 mg, 1 286 mmol) [sample temp 105-130 °C, oven temp 540 °C, p 1 10^{-2} mm Hg, cold trap temp -196 °C] produced **6b** (244 mg, 89 %) as a NMR-pure white-yellow solid M p 109-112 °C (after recrystallization from EtOAc /*n*-hexane = 1/3 or CH_2Cl_2/*n*-hexane = 1/5) ^{1}H-NMR δ 2 76-2 93 (m, 2H, H_8), 2 93-3 09 (m, 2H, H_7), 6 19 (t, J=2 7 Hz, 1H, H_4), 7 39 (s, 5H, Ph), ^{13}C-NMR δ 20 8 (t, C_8), 41 8 (t, C_7), 79 7 (d, C_4), 125 8 (d), 128 9 (d), 129 2 (d, Ph), 133 2 (s, Ph), 163 6 (s), 165 9 (s), 167 0 (s, C_1, C_2, C_5), 198 4 (s, C_6), IR (KBr) ν 1762 (C=O, lactone), 1710 (C=O, enone), 1190, 1050 cm^{-1}, EI/MS m/e 214 (M^+), 172 (M-$COCH_2^+$), 105 ($C_6H_5CO^+$), 77, 51, UV (MeOH) λ_{max} 235 nm (13000), Found 214 0622 $C_{13}H_{10}O_3$ requires 214 0630 Found C, 72 57, H, 4 66 $C_{13}H_{10}O_3$ requires C, 72 89, H, 4 71

2,6-*Dioxo*-4-n-*hexyl*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **6c**

FVT of **4c** (200 mg, 0 694 mmol) [sample temp 110 °C, oven temp 520 °C, p 2 10^{-2} mm Hg, cold trap temp -78 °C] produced **6c** (140 mg, 91 %) as a NMR-pure white solid M p 47-49 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 0 76-1 02 (m, 3H, CH_3), 1 16-2 11 (m, 10H, C_4-$(CH_2)_5$), 2 71-2 89 (m, 2H, H_8), 2 91-3 09 (m, 2H, H_7), 5 03-5 30 (m, 1H, H_4), ^{13}C-NMR δ 13 8 (CH_3), 21 1, 22 3, 24 5, 28 6, 31 3, 32 6 (C_4-C(CH_2)$_5$, C_8), 41 9 (C_7), 79 6 (C_4), 164 2, 167 0, 167 4 (C_1, C_2, C_5), 198 9 (C_6), IR (KBr) ν 1757 (C=O, lactone), 1710 (C=O, enone), 1195 cm^{-1}, EI/MS m/e 222 (M^+), 178 (M-CO_2), 138 (M-$C_6H_{13}^+$+1), Found 222 1250 $C_{13}H_{18}O_3$ requires 222 1256 Found C, 70 33, H, 8 03 $C_{13}H_{18}O_3$ requires C, 70 24, H, 8 16

4,4-*Dimethyl*-2,6-*dioxo*-3-*oxabicyclo*[3 3.0]*oct*-1(5)-*ene* **6d**

FVT of **4d** (290 mg, 1 25 mmol) [sample temp 85-100 °C, oven temp 520 °C, p 2 10^{-2} mm Hg, cold trap temp -78 °C] gave **6d** (207 mg, 100 %) as a NMR-pure white solid, Rf = 0 4 (silica gel, EtOAc /*n*-hexane = 1/1, I_2) M p 60-62 °C (after recrystallization from CH_2Cl_2 /*n*-hexane = 1/10) ^{1}H-NMR δ 1 59 (s, 6H, C_4-$(CH_3)_2$), 2 69-2 84 (m, 2H, H_8), 2 91-3 04 (m, 2H, H_7), ^{13}C-NMR δ 20 6 (t, C_8), 24 6 (q, C_4-$(CH_3)_2$), 41 8 (t, C_7), 83 8 (s, C_4), 162 9 (s), 166 7 (s), 170 2 (s, C_1, C_2, C_5), 198 8 (s, C_6), IR (KBr) ν 1764 (C=O, lactone), 1714 (C=O, enone), 1328, 1050 cm^{-1}, EI/MS m/e 166 (M^+), 151 ($M-CH_3^+$), 124, 123 ($M-COCH_3^+$), 43 ($COCH_3^+$), UV (MeOH) λ_{max} 235 nm (26000), Found C, 64 93, H, 6 10 $C_9H_{10}O_3$ requires C, 65 05, H, 6 07

2,6-*Dioxo*-cis-8-*methyl*-4-*phenyl*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **6e**

FVT of **4e** (172 mg, 0 585 mmol) [sample temp 110 °C, oven temp 500 °C, p 2 10^{-2} mm Hg, cold trap temp -78 °C] yielded **6e** (128 mg, 96 %) as a NMR-pure oil, Rf = 0 25 (silica gel, EtOAc /*n*-hexane = 1/2) ^{1}H-NMR δ 1 40 (d, J=6 8 Hz, 3H, CH_3), 2 56 A of ABX (dd, J_{AB}=21 0 Hz, J_{AX}=4 0 Hz, 1H, H_7), 3 16-3 42 X of ABX (m, 1H, H_8), 3 26 B of ABX (dd, J_{AB}=21 0 Hz, J_{BX}=5 9 Hz, 1H, H_7), 6 18 (d, J=3 0 Hz, 1H, H_4), 7 38 (s, 5H, C_4-Ph), ^{13}C-NMR (200 MHz) δ 18 0 (CH_3), 29 3 (C_8), 50 7 (C_7), 79 2 (C_4), 125 9, 128 8, 129 0, 133 2 (Ph), 165 1, 166 8 (C_1, C_2, C_5), 198 0 (C_6), IR (CCl_4) ν 1775 (C=O, lactone), 1720 (C=O, enone), 1033 cm^{-1}, EI/MS m/e 228 (M^+), 213 ($M-CH_3^+$), 105 ($C_6H_5CO^+$), Found 228 0790 $C_{14}H_{12}O_3$ requires 228 0786

Cis-8-n-*butyl*-2,6-*dioxo*-4-*phenyl*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **6f**

FVT of **4f** (520 mg, 1 548 mmol) [sample temp 130 °C, oven temp 500 °C, p 2 10^{-2} mm Hg, cold trap temp -78 °C] gave **6f** (410 mg, 98 %) as a NMR-pure oil ^{1}H-NMR δ 0 80-1 07 (m, 3H, C_8-$(CH_2)_3CH_3$), 1 16-2 20 (m, 6H, C_8-$(CH_2)_3$), 2 61 A of ABX (dd, J_{AB}=20 8 Hz, J_{AX}=4 0 Hz, 1H, H_7), 3 04-3 33 X of ABX (m, 1H, H_8), 3 17 B of ABX (dd, J_{AB}=20 8 Hz, J_{BX}=6 0 Hz, 1H, H_7), 6 18 (d, J=3 0 Hz, 1H, H_4), 7 39 (s, 5H), ^{13}C-NMR (200 MHz) δ 13 6 (CH_3), 22 3, 29 4, 32 3 (C_8-$(CH_2)_3$), 34 8 (C_8), 48 5 (C_7), 79 3 (C_4), 125 9, 128 7, 129 0, 133 2 (Ph), 165 3, 166 0, 166 8 (C_1, C_2, C_5), 198 0 (C_6), IR (CCl_4) ν 2960, 2930, 1775 (C=O, lactone), 1722 (C=O, enone), 1190, 1002 cm^{-1}, EI/MS m/e 270 (M^+), 214 ($M+1-C_4H_9$), 105 ($C_6H_5CO^+$), Found 270 1243 $C_{17}H_{18}O_3$ requires 270 1256

2,6-*Dioxo*-trans-8-*methyl*-4-*phenyl*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **6g**

FVT of **4g** (33 mg, 0 112 mmol) [sample temp 110 °C, oven temp 520 °C, p 2 10^{-2} mm Hg, cold trap temp -78 °C] gave **6g** (21 mg, 82 %) as a NMR-pure white solid, Rf = 0 30 (silica gel, EtOAc /*n*-hexane = 1/2) M p 155-160 °C (after recrystallization from *n*-hexane /CH_2Cl_2 = 3/1) ^{1}H-NMR δ 1 42 (d, J=6 9 Hz, 3H, CH_3), 2 60 A of ABX (dd, J_{AB}=21 1 Hz, J_{AX}=3 9 Hz, 1H, H_7), 3 16-3 42 X of ABX (m, 1H, H_8), 3 24 B of ABX (dd, J_{AB}=21 1 Hz, J_{BX}=6 0 Hz, 1H, H_7), 6 20 (d, ^{5}J=1 6 Hz, 1H, H_4), 7 40 (s, 5H, Ph), IR (KBr) ν 2960, 1752 (C=O, lactone), 1715 (C=O, enone), 1460, 1330, 1205 cm^{-1}, EI/MS m/e 228 (M^+), 213 ($M-CH_3^+$), 186, 105 ($C_6H_5CO^+$), 77, 51, UV (MeOH) λ_{max} 238 nm

(12000); Found 228.0790. $C_{14}H_{12}O_3$ requires 228.0786. Found C, 73.37; H, 5.25. $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.30.

2,6-*Dioxo*-4,4,8-*trimethyl*-3-*oxabicyclo*[3.3.0]*oct*-1(5)-*ene* **6h**

FVT of **4h** (500 mg, 2.033 mmol) [sample temp.: 125-130 °C, oven temp.: 500 °C, p: 2.10^{-2} mm Hg, cold trap temp.: -78 °C] gave **6h** (370 mg, 100 %) as a NMR-pure white solid. M.p. 104-106 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.37 (d, J=6.9 Hz, 3H, C_8-CH_3), 1.58 (s, 6H, 2xC_4-Me), 2.52 A of ABX (dd, J=21 Hz, J=4.1 Hz, 1H, H_7), 3.04-3.40 BX of ABX (m, 2H, H_7, H_8); IR (KBr): ν 1765, 1755 (C=O, lactone), 1705 (C=O, enone), 1335, 1045 cm^{-1}; EI/MS: m/e 180 (M^+), 165 (M-CH_3^+), 137 (M-CH_3^+-CO), 107, 93; UV (MeOH): λ_{max} 237 nm (12000); Found 180.0790. $C_{10}H_{12}O_3$ requires 180.0786. Found C, 66.34; H, 6.75. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71. **6h** was also prepared in the same manner from **4i** (50 mg, 0.205 mol) to yield 37 mg **6h** (100 %) as a crude white-yellow solid (m.p. 88-99 °C). Subsequent recrystallization from *n*-hexane afforded pure **6h**.

4,4-*Dimethyl*-2,6-*dioxo*-8-n-*butyl*-3-*oxabicyclo*[3.3.0]*oct*-1(5)-*ene* **6j**

FVT of **4j** (560 mg, 1.944 mmol) [sample temp.: 110 °C, oven temp.: 520 °C, p: 2-4.10^{-2} mm Hg, cold trap temp.: -78 °C] afforded **6j** (406 mg, 94 %) as a NMR-pure oil, purity by CapGC 97 %. ^{1}H-NMR: δ 0.80-1.02 (m, 3H, C_8-$(CH_2)_3CH_3$), 1.18-1.54 (m, 4H, C_8-$CH_2(CH_2)_2$), 1.58 (s, 6H, C_4-$(CH_3)_2$), 1.77-2.15 (m, 2H, C_8-CH_2), 3.11 A of ABX (dd, J_{AB}=20.8 Hz, J_{AX}=3.8 Hz, 1H, H_7), 2.93-3.28 B and X of ABX (dd, J_{AB}=20.8 Hz, J_{BX}=5.6 Hz, 1H, H_7 and m, 1H, H_8); IR (CCl_4): ν 2935, 1769 (C=O, lactone), 1720 (C=O, enone), 1050 cm^{-1}; EI/MS: m/e 222 (M^+), 165 (M-$C_4H_9^+$); Found 222.1255. $C_{13}H_{18}O_3$ requires 222.1256.

Trans-8-n-*butyl*-2,6-*dioxo*-4-*phenyl*-3-*oxabicyclo*[3.3.0]*oct*-1(5)-*ene* **6k**

Flash chromatography of **6f** (silica gel, EtOAc /*n*-hexane = 1/2) gave a mixture of **6k** and **6f** in a molar ratio of 1:3. **6k**: m.p. 76-78 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 0.80-1.07 (m, 3H, C_8-$(CH_2)_3CH_3$), 1.18-2.18 (m, 6H, C_8-$(CH_2)_3$), 2.64 A of ABX (dd, J_{AB}=20.8 Hz, J_{AX}=4.0 Hz, 1H, H_7), 3.02-3.31 X of ABX (m, 1H, H_8), 3.14 B of ABX (dd, J_{AB}=20.8 Hz, J_{BX}=6.0 Hz, 1H, H_7), 6.19 (d, ^{5}J=1.2 Hz, 1H, H_4), 7.39 (s, 5H, Ph); IR (KBr): ν 1760, 1705, 1195 cm^{-1}; EI/MS: m/e 270 (M^+), 214 (M+1-C_4H_9), 105 (C_6H_5CO); UV (MeOH): λ_{max} 238 nm (10300); Found C, 75.12; H, 6.74. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71.

Hydrogenation of ethyl 3-oxocyclopent-1-*ene carboxylate*

Ethyl 3-oxocyclopent-1-ene carboxylate[13] (55 mg, 0.357 mmol) (that was obtained in quantitative yield from ethyl 5-oxo-*endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-ene 2-carboxylate (compound **28** in Chapter 3) using FVT [oven temp.: 500 °C, p: 2.10^{-2} torr]) was catalytically hydrogenated (Pd/C) in isopropanol at r.t. for 15 min to yield *ethyl 3-oxocyclopentane carboxylate*[23] (50 mg, 90 %) as a NMR-pure oil. ^{1}H-NMR: δ 1.28 (t, J= 7.1 Hz, 3H, CH_3), 1.93-2.58 (m, 6H, H_2, H_4, H_5), 2.93-3.36 (m, 1H, H_1), 4.19

(q, J=7.1 Hz, 2H, OCH_2); IR (CCl_4): ν 2980, 1745 (C=O, ketone), 1730 (C=O, ester), 1190, 1155 cm^{-1}; EI/MS: m/e 156 (M^+), 128 (M-CO), 111, 100, 83 (M-COOEt); Found 156.0791. $C_8H_{12}O_3$ requires 156.0786.

2,6-*Dioxo*-cis-3-*oxabicyclo*[3.3.0]*octane (cyclosarkomycin)* **11a**

Zinc dust (100 mg, 1.53 mmol) was added to a stirred soln of **6a** (20 mg, 0.145 mmol) in AcOH (4 ml) under a N_2 atmosphere at r.t. The temperature was slowly raised to 105 °C. The reaction was monitored by CapGC. After 4 h at 105 °C, the mixture was cooled to r.t. and an excess of $NaHCO_3$ aq was added. The resulting mixture was extracted with Et_2O (3x), washed (H_2O), dried ($MgSO_4$) and evaporated *in vacuo*, to yield **11a** (17 mg, 84 %) as a NMR-pure oil. Flash chromatography (silica gel, Rf = 0.35, EtOAc, I_2) gave **11a** (99.8 % purity by CapGC) which slowly solidified on stirring in *n*-hexane. M.p. 40-47 °C (lit.[3] 45-47 °C, *n*-hexane). The spectral data were in good agreement with those reported by Smith *et al*[3]. ^{1}H-NMR: δ 2.00-2.64 (m, 4H, H_7, H_8), 2.91-3.16 (m, 1H, H_5), 3.27-3.54 (m, 1H, H_1), 4.30-4.55 (m, 2H, H_4), $^3J_{1,5}$=9 Hz (determined by decoupling at H_4); IR (CCl_4): ν 2930, 1780 (C=O, lactone), 1750 (C=O, ketone), 1150, 1030 cm^{-1}; EI/MS: m/e 140 (M^+), 96 (M-CO_2), 85 ($C_5H_9O^+$), 68, 54; Found 140.0467. $C_7H_8O_3$ requires 140.0473.

4,4-*Dimethyl*-2,6-*dioxo*-cis-3-*oxabicyclo*[3.3.0]*octane* **11d**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (200 mg, 3.06 mmol) and **6d** (80 mg, 0.482 mmol) in AcOH (6 ml) was stirred for 1 h at 50 °C to yield **11d** (53 mg, 65 %) as a white solid which was purified by flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1, Rf = 0.22, I_2); 100 % purity by CapGC. M.p. 69-71 °C (after recrystallization from CH_2Cl_2/*n*-hexane = 1/20). ^{1}H-NMR: δ 1.43 (s, 3H, C_4-Me), 1.47 (s, 3H, C_4-Me), 1.98-2.56 (m, 4H, H_7, H_8), 2.68 (d, J=8.9 Hz, 1H, H_5), 3.42-3.67 (m, 1H, H_1); IR (CCl_4): ν 1777 (C=O, lactone), 1745 (C=O, ketone), 1260, 1130, 1100 cm^{-1}; EI/MS: m/e 168 (M^+), 153 (M-CH_3^+), 82; Found 168.0786. $C_9H_{12}O_3$ requires 168.0786.

2,6-*Dioxo*-exo-4-*phenyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11bI**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (100 mg, 1.53 mmol) and **6b** (30 mg, 0.14 mmol) in AcOH (4 ml) was stirred for 45 min at 50-60 °C to yield **11bI** (20 mg, 66 %, 93 % purity by CapGC) after flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1, Rf = 0.4, I_2). M.p. 66-66.5 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.98-2.73 (m, 4H, H_7, H_8), 3.00 (dd, J=9.0 Hz, J=1.8 Hz, 1H, H_5), 3.31-3.62 (m, 1H, H_1), 5.59 (d, J=1.8 Hz, 1H, H_4), 7.26-7.44 (m, 5H, Ph); IR (CCl_4): ν 1785 (C=O, lactone), 1750 (C=O, ketone), 1140, 695 cm^{-1}; EI/MS: m/e 216 (M^+), 130, 105 ($C_6H_5CO^+$), 83, 77; Found 216.0790. $C_{13}H_{12}O_3$ requires 216.0786.

Stereoselective reduction of **6c**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (150 mg, 2.29 mmol) **6c** (90 mg, 0.405 mmol) in AcOH (5 ml) was stirred for 90 min at 75 °C to yield a crude mixture of 2,6-*dioxo*-exo-4-n-*hexyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11cI** and 2,6-*dioxo*-endo-4-n-*hexyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11cII** (71 mg, 78 %) in a ratio of in a ratio of 2:1 (^{1}H-NMR) as a viscous oil which was purified by flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1, Rf = 0.38, I_2). ^{1}H-NMR: δ 0.73-1.85 (m, 13H, C_4-$(CH_2)_5CH_3$), 2.00-2.58 (m, 4H, H_7, H_8), 2.73 (dd, J=9.0 Hz, J=1.6 Hz, 1H, H_5 (**11cI**)), 2.98 (br d, J=6.6 Hz, 1H, H_5 (**11cII**)), 3.27-3.58 (m, 1H, H_1), 4.42-4.69 (m, 1H, H_4); IR (CCl_4): ν 1780 (C=O, lactone), 1745 (C=O, ketone) cm^{-1}; EI/MS: m/e 224 (M^+), 180 (M-CO_2), 139 (M-$C_6H_{13}^+$), 83 ($C_5H_7O^+$); Found 224.1408. $C_{13}H_{20}O_3$ requires 224.1412.

Stereoselective reduction of **6h**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (300 mg, 4.59 mmol) **6h** (260 mg, 1.44 mmol) in AcOH (10 ml) was stirred for 1 h at 50 °C to yield **11hII** and **11hI** (180 mg, 68 %) in a ratio of 8:1 (CapGC). Recrystallization from *n*-hexane afforded analytically pure 2,6-*dioxo*-4,4-*dimethyl*-endo-8-*methyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11hII**: 100 % purity by CapGC. M.p. 100-102.5 °C. ^{1}H-NMR: δ 1.29-1.51 (m, 9H, 3xCH_3), 1.84-2.18 (m, 1H, H_7), 2.27-2.82 (m, 3H, H_5, H_7, H_8), 3.44 (br t, J=8 Hz, 1H, H_1); IR (KBr): ν 1760, 1750 (C=O, lactone), 1728 (C=O, ketone), 1260, 1170, 1140, 1110, 1090 cm^{-1}; EI/MS: m/e 182 (M^+), 167 (M-CH_3^+), 96 (M-$(CH_3)_2$COCO); Found C, 65.75; H, 7.76. $C_{10}H_{14}O_3$ requires C, 65.92; H, 7.74. 2,6-*Dioxo*-4,4-*dimethyl*-exo-8-*methyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11hI** was characterized by its mass spectrum which closely corresponded to that of **11hII**: CapGC/EI/MS: m/e 182, 167, 96.

Endo-8-n-*butyl*-2,6-*dioxo*-4,4-*dimethyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11jII**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (630 mg, 9.64 mmol) and **6j** (406 mg, 1.83 mmol) in AcOH (10 ml) was stirred for 3 h at 60 °C to yield **11jII** (295 mg, 72 %) as a NMR-pure white solid which was purified by recrystallization from *n*-hexane. M.p. 74-76 °C. ^{1}H-NMR: δ 0.80-1.04 (m, 3H, C_8-$(CH_2)_3CH_3$), 1.20-2.62 (m, 15H, C_8-$(CH_2)_3$, 2xC_4-CH_3, H_7, H_8), 2.71 (d, J=8.8 Hz, 1H, H_5), 3.53 (br t, J≅8.5 Hz, 1H, H_1); ^{13}C-NMR: δ 13.7 (C_8-$(CH_2)_3CH_3$), 22.2, 23.7, 29.8, 30.1 (C_4-$(CH_3)_2$, C_8-$(CH_2)_3$), 38.0 (C_8), 45.0, 45.6 (C_5, C_7), 57.6 (C_1), 82.8 (C_4), 174.1 (C_2), 213.0 (C_6); IR (KBr): ν 2960, 1755 (C=O, lactone), 1735 (C=O, ketone), 1480, 1392, 1372, 1120 cm^{-1}; EI/MS: m/e 224 (M^+), 167 (M-$C_4H_9^+$), 113; Found C, 69.48; H, 8.98. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99.

Stereoselective reduction of **6e**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (190 mg, 2.91 mmol) and **6e** (97 mg, 0.425 mmol) in AcOH (3 ml) was stirred for 1h at 38 °C to yield **11eI**, **11g** and **11eII** (83 mg, 85 %) in a ratio of 6:2:1 (CapGC). Separation by flash chromatography (silica

gel, EtOAc /*n*-hexane = 1/1) gave pure **11eI** and **11eII**. 2,6-*Dioxo*-exo-8-*methyl*-exo-4-*phenyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11eI**: Rf = 0.45 (silica gel, EtOAc /*n*-hexane = 1/1, I_2). M.p. 115-117 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.23 (d, J=7.0 Hz, 3H, CH_3), 2.18 A of ABX (dd, J_{AB}=18.4 IIz, J_{AX}=4.2 Hz, 1H, H_7), 2.57 B of ABX (dd, J_{AB}=18.4 Hz, J_{BX}=7.2 Hz, 1H, H_7), 2.71-3.04 (m, 1H, H_8), 3.11 (br s, 2H, H_1, H_5), 5.57 (br s, 1H, H_4), 7.35 (s, 5H, Ph); IR (KBr): ν 1770 (C=O, lactone), 1735 (C=O, ketone), 1450, 1172, 1025 cm^{-1}; EI/MS: m/e 230 (M^+), 160, 129; Found C, 72.60; H, 6.11. $C_{14}H_{14}O_3$ requires C, 73.03; H, 6.13.

2,6-*Dioxo*-endo-8-*methyl*-endo-4-*phenyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11eII**: Rf = 0.2 (silica gel, EtOAc /*n*-hexane = 1/1), purity by CapGC >98 %. M.p. 124-126 °C (after recrystallization from EtOAc /*n*-hexane = 1/10). ^{1}H-NMR: δ 1.44 (d, J=6.6 Hz, 3H, CH_3), 1.76-2.02 (m, 1H, H_7), 2.18-2.73 (m, 2H, H_7, H_8), 3.29 (dd, J=8 Hz, J=7.7 Hz, 1H, H_5), 3.44 (dd, J=8 Hz, J=8 Hz, 1H, H_1), 5.69 (d, J=7.7 Hz, 1H, H_4), 7.11-7.44 (m, 5H, Ph); IR (KBr): ν 2870, 1775 (C=O, lactone), 1727 (C=O, ketone), 1260, 1185, 1030 cm^{-1}; EI/MS: m/e 230 (M^+), 144, 124 (M-C_6H_5CHO); Found 230.0940. $C_{14}H_{14}O_3$ requires 230.0943. Found C, 72.27; H, 6.09. $C_{14}H_{14}O_3$ requires C, 73.03; H, 6.13.

Stereoselective reduction of **6g**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (30 mg, 0.46 mmol) and **6g** (17 mg, 0.075 mmol) in AcOH (2 ml) was stirred for 1h at 38 °C to yield **11g** (13 mg, 75 %) as a white solid which was purified by flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1, Rf = 0.4). 2,6-*Dioxo*-endo-8-*methyl*-exo-4-*phenyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11g**: m.p. 66-67 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.41 (d, J=6.6 Hz, 3H, CH_3), 2.07 A of ABX (dd, J_{AB}=20.0 Hz, J_{AX}=12.8 Hz, 1H, H_7), 2.49-2.83 (m, 2H, H_7, H_8), 3.09 (br d, J=9 Hz, 1H, H_5), 3.40 (dd, J=9 Hz, J=8 Hz, 1H, H_1), 5.55 (d, J=2.0 Hz, 1H, H_4), 7.37 (s, 5H, Ph); CapGC/EI/MS: m/e 230 (M^+), 160, 129.

Stereoselective reduction of **6f**

The same procedure as described for the reduction of **6a** was employed. A suspension of zinc (203 mg, 3.10 mmol) and **6f** (204 mg, 0.756 mmol) in AcOH (10 ml) was stirred for 30 min at 45 °C to yield **11fI**, **11k** and **11fII** (143 mg, 69 %) in a ratio of 9:3:4 (CapGC). Separation by flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3) gave pure **11fI** and **11fII**. Exo-8-n-*butyl*-2,6-*dioxo*-exo-4-*phenyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11fI**: Rf = 0.38 (silica gel, EtOAc /*n*-hexane = 1/3). M.p. 66-67 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 0.78-1.04 (m, 3H, CH_3), 1.18-1.62 (m, 6H, C_8-$(CH_2)_3$), 2.09-2.38 (m, 1H, H_7), 2.54 (d, J=7.2 Hz, 1H, H_7), 2.60-2.82 (m, 1H, H_8), 3.02 (br d, J=9.2 Hz, 1H, H_5), 3.20 (br d , J=9.2 Hz, 1H, H_1), 5.58 (d, J=1.8 Hz, 1H, H_4), 7.36 (s, 5H, Ph); IR (KBr): ν 2955, 2920, 1775 (C=O, lactone), 1737 (C=O, ketone), 1235, 1195, 1190, 997 cm^{-1}; EI/MS: m/e 272 (M^+), 139 (M-$C_6H_5COCO^+$); Found C, 74.35; H, 7.46. $C_{17}H_{20}O_3$ requires C, 74.97; H, 7.40. Endo-8-n-*butyl*-2,6-*dioxo*-exo-4-*phenyl*-cis-3-*oxabicyclo*[3.3.0]*octane* **11k**: (Some of the ^{1}H-NMR spectral data of **11k** were deduced from a mixture of **11fI** and **11k**): ^{1}H-NMR: δ 3.29 (br d, J=8 Hz,

1H, H_1), 3 49 (br d, J=8 Hz, 1H, H_5) Endo 8-n *butyl*-2,6-*dioxo*-endo-4-*phenyl*-cis 3 *oxabicyclo*-[3 3 0]*octane* **11fII** Rf = 0 2 (silica gel, EtOAc /*n*-hexane = 1/3) M p 86-88 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 0 82-1 04 (m, 3H, CH_3), 1 18-2 56 (m, 9H, C_8-$(CH_2)_3$, H_7, H_8), 3 30 (q, J≅9 Hz, 1H, H_5), 3 49 (dd, J≅9 Hz, J≅7 5 Hz, 1H, H_1), 5 67 (d, J=8 2 Hz, 1H, H_4), 7 40 (m, 5H, Ph), IR (CCl_4) ν 1777 (C=O, lactone), 1750 (C=O, ketone), 1165 cm^{-1}, EI/MS m/e 272 (M^+), 186, 166 (M-C_6H_5CHO), 139 (M $C_6H_5COCO^+$), Found 272 1392 $C_{17}H_{20}O_3$ requires 272 1412

2-Isopropylidene-3-oxocyclopentane carboxylic acid (dimethylsarkomycin) **17d**

To a suspension of zinc dust (200 mg, 3 06 mmol) in AcOH (6 ml) was added **6d** (80 mg, 0 482 mmol) The temperature was very quickly raised to 90 °C After 15 min reaction at 90 °C, the reaction mixture was cooled to r t and an excess of $NaHCO_3$ aq was added The resulting mixture was extracted with Et_2O (3x) The combined ether extracts were washed (H_2O), dried ($MgSO_4$) and evaporated *in vacuo*, to yield **11d** (30 mg, 37 %) as a white solid The remaining aqueous phase of the previous extraction was acidified to pH 1 by slow addition of aqueous HCl and thrice extracted with Et_2O (acid base extraction) The combined ether extracts were washed (H_2O), dried ($MgSO_4$) and evaporated *in vacuo*, to afford **17d** (50 mg, 62 %) as a NMR-pure solid M p 93-96 °C (after recrystallization from $CCl_4/CHCl_3$ = 3/1) (lit[24] 101 °C (C_6H_6/ligroin)) ^{1}H-NMR δ 1 96 (s, 3H, C_2-$C(CH_3)$), 2 02-3 04 (m, 7H, C_2-$C(CH_3)$, H_4, H_5), 3 84 (d, J=7 2 Hz, 1H, H_1), 7 11-8 27 (br s, 1H, C_1-COOH), IR (CCl_4) ν 3550-2500 (COOH), 1740 (C=O, ketone), 1705 (C=O, acid), 1627 (C=C), 1408, 1177 cm^{-1}, EI/MS m/e 168 (M^+), 123 (M-COOH), 95, Found 168 0782 $C_9H_{12}O_3$ requires 168 0786

Reduction and eliminative ringopening of **6h**

The same procedure as described for the preparation of **17d** was employed A suspension of zinc dust (300 mg, 4 59 mmol) and **6h** (260 mg, 1 444 mmol) in AcOH (10 ml) was reacted for 1 h at 50 °C, to yield a mixture of **17hI** and **17hII** (80 mg, 30 %) after acid-base extraction in a ratio of 3 1 The yield of **17hI** and **17hII** was not optimized (*e g* by applying higher temperatures) M p 60-85 °C (diastereomeric mixture, molar ratio of 4 1 after recrystallization from *n*-hexane) *2-Isopropylidene-cis-5-methyl-3-oxocyclopentane carboxylic acid* **17hI** ^{1}H-NMR δ 1 06-1 27 (m, 3H, C_5-CH_3), 1 91 (m, 3H, C_2-$C(CH_3)$), 2 27 (s, 3H, C_2-$C(CH_3)$), 2 36 3 02 (m, 3H, H_4, H_5), 3 73 (br s, 1H, H_1), 6 50 8 50 (br s, 1H, C_1-COOH), IR (KBr) ν 3500-2500 (COOH), 1705 (C=O, ketone), 1690 (C=O, acid), 1627 (C=C), 1225, 1185 cm^{-1}, CapGC/EI/MS m/e 182 (M^+), 167 (M-CH_3), 137 (M-COOH), Found C, 65 76, H, 7 70 $C_{10}H_{14}O_3$ requires C, 65 92, H, 7 74 *2-Isopropylidene-trans-5-methyl-3-oxocyclopentane carboxylic acid* **17hII** This acid was not isolated but was characterized by its mass spectral data, CapGC/EI/MS m/e 182 (M^+), 167 (M-CH_3), 96

Reduction and eliminative ringopening of **6j**

The same procedure was used as described for the preparation of **11jII** The acids **17jI** and **17jII** (108 mg, 26 %) were isolated after acid-base extraction as a 2 1 diastereomeric mixture (^{1}H-NMR,

CapGC). Cis-5-n-*butyl*-2-*isopropylidene*-3-*oxocyclopentane carboxylic acid* **17jI**: ^{1}H-NMR: δ 0.78-1.07 (m, 3H, C_5-$(CH_2)_3CH_3$), 1.16-1.71 (m, 6H, C_5-$(CH_2)_3$), 1.91 (s, 3H, C_2-CCH_3), 2.18-2.60 (m, 6H, C_2-CCH_3, H_4, H_5), 3.79 (br d, J=6 Hz, 1H, H_1), 7.60-8.60 (br s, 1H, C_1-COOH); IR (CCl_4): ν 3550-2400 (COOH), 1700 (C=O, ketone), 1630 (C=C) cm^{-1}; CapGC/EI/MS: m/e 224 (M^+), 209 (M-CH_3), 179 (M-COOH), 167 (M-C_4H_9); Found 224.1408. $C_{13}H_{20}O_3$ requires 224.1412. Trans-5-n-*butyl*-2-*isopropylidene*-3-*oxocyclopentane carboxylic acid* **17jII**: This acid was not isolated but was characterized by its mass spectral data; CapGC/EI/MS: m/e 224 (M^+), 209 (M-CH_3), 179 (M-COOH), 167 (M-C_4H_9).

Methyl 2-*isopropylidene*-3-*oxocyclopentane carboxylate* **18d**

A soln of **17d** (46 mg, 0.274 mmol) in CH_2Cl_2 was treated with CH_2N_2 (0.3 M in Et_2O) at r.t. for 15 min. Removal of the solvents and flash chromatography (silica gel, EtOAc /*n*-hexane = 1/2) of the residue gave pure **18d** (46 mg, 92 %) as an oil (purity by Cap GC 99 %). ^{1}H-NMR: δ 1.91 (s, 3H, C_2-$C(CH_3)$), 1.98-2.80 (m, 7H, C_2-$C(CH_3)$, H_4, H_5), 3.70 (s, 3H, OCH_3), 3.84 (br d, J=7.5 Hz, 1H, H_1); IR (CCl_4): ν 2950, 1732 (C=O, ester), 1710 (C=O), 1627 (C=C), 1165 cm^{-1}; EI/MS: m/e 182 (M^+), 123 (M-COOMe), 95; Found 182.0941. $C_{10}H_{14}O_3$ requires 182.0943.

Esterification of **17jI** *and* **17jII**

A mixture of **17jI** and **17jII** (92 mg, 0.411 mmol) in CH_2Cl_2 was treated with CH_2N_2 (0.3 M in Et_2O) at r.t. for 15 min to afford NMR-pure **18jI** and a mixture of **18jI** and **18jII** (total yield: 88 mg, 90 %) after flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3, Rf = 0.35). *Methyl* cis-5-n-*butyl*-2-*isopropylidene*-3-*oxocyclopentane carboxylate* **18jI**: ^{1}H-NMR: δ 0.78-1.04 (m, 3H, C_5-$(CH_2)_3CH_3$), 1.18-1.51 (m, 6H, C_5-$(CH_2)_3$), 1.87 (s, 3H, C_2-CCH_3), 2.18-2.56 (m, 6H, C_2-CCH_3, H_4, H_5), 3.71 (s, 3H, OMe), 3.82 (br d, J=7 Hz, 1H, H_1); IR (CCl_4): ν 2960, 2935, 1735 (C=O, ester), 1710 (C=O), 1632 (C=C) cm^{-1}; CapGC/EI/MS: m/e 238 (M^+), 223 (M-CH_3), 179 (M-COOMe). *Methyl* trans-5-n-*butyl*-2-*(isopropylidene)*-3-*oxocyclopentane carboxylate* **18jII**: Characteristic ^{1}H-NMR absorptions: δ 2.09 A of ABX (dd, J=17 Hz, J=3 Hz, 1H, H_4), 2.20-2.49 (m, 4H, C_2-CCH_3, H_5), 2.79 B of ABX (dd, J=17 Hz, J=8 Hz, 1H, H_4), 3.49 (br s, 1H, H_1), 3.72 (s, 3H, OMe); CapGC/EI/MS: m/e 238 (M^+), 223 (M-CH_3), 179 (M-COOMe); Found 238.1554. $C_{14}H_{22}O_3$ requires 238.1569.

2-*Benzyl*-3-*oxocyclopentane carboxylic acid* **20b**

The same procedure as described for the preparation of **17d** was employed. A suspension of zinc dust (600 mg, 9.18 mmol) and **6b** (480 mg, 2.243 mmol) in AcOH (15 ml) was reacted for 1 h at 60-70 °C, to yield **11bI** (131 mg, 27 %). Acid **20b** (323 mg, 66 %) was isolated after acid-base extraction as a diastereomeric mixture. ^{1}H-NMR: δ 1.49-3.07 (m, 8H, H_1, H_2, H_4, H_5, C_2-CH_2), 6.00-7.00 (br s, 1H, C_1-COOH), 7.09-7.31 (m, 5H, Ph); IR (CCl_4): ν 3600-2500 (COOH), 1750 (C=O, ketone), 1700 (C=O, acid), 700 cm^{-1}; CapGC/EI/MS: m/e 218 (M^+), 173 (M-COOH), 91.

2-Benzyl-5-methyl-3-oxocyclopentane carboxylic acid **20e**

The same procedure as described for the preparation of **17d** was employed. A suspension of zinc dust (300 mg, 4.59 mmol) and **6e** (283 mg, 1.241 mmol) in AcOH (5 ml) was reacted for 1 h at 62 °C, to yield a mixture of **11eI**, **11g** and **11eII** (80 mg, 28 %) together with **20e** (199 mg, 69 %). Acid **20e** was isolated after acid-base extraction as a diastereomeric mixture. CapGC/MS showed all diastereomers to have almost identical mass spectra. IR (CCl_4): ν 3500-2500 (COOH), 1745 (C=O, ketone), 1705 (C=O, acid), 1260 cm^{-1}; MS: m/e 232 (M^+), 187 (M-COOH), 91; Found 232.1100. $C_{14}H_{16}O_3$ requires 232.1100.

2-Benzyl-5-n-butyl-3-oxocyclopentane carboxylic acid **20f**

The same procedure as described for the preparation of **17d** was employed. A suspension of zinc dust (405 mg, 6.19 mmol) and **6f** (410 mg, 1.52 mmol) in AcOH (10 ml) was reacted for 4 h at 90 °C, to yield a mixture of **11fI**, **11k** and **11fII** (260 mg, 63 %) and **20f**. Acid **20f** (102 mg, 25 %) was isolated after acid-base extraction (pH=1, Et_2O) as a diastereomeric mixture (oil). CapGC/MS showed that all diastereomers had almost identical mass spectra. ^{1}H-NMR: δ 0.73-0.99 (m, 3H, CH_3), 1.02-1.56 (m, 6H, C_5-$(CH_2)_3$), 2.11-2.62 (m, 4H, H_2, H_4, H_5), 2.78-3.40 (m, 3H, H_1, C_2-CH_2), 7.02-7.33 (m, 5H, Ph), 8.53 (br s, 1H, COOH); IR (CCl_4): ν 3500-2500 (COOH), 2960, 2930, 1745 (C=O, ketone), 1705 (C=O, acid), 1240 cm^{-1}; EI/MS: m/e 274 (M^+), 229 (M-COOH), 91; Found 274.1561. $C_{17}H_{22}O_3$ requires 274.1570.

Methyl 2-benzyl-3-oxocyclopentane carboxylate **21b**

A soln of **20b** (93 mg, 0.427 mmol) in CH_2Cl_2 was reacted with CH_2N_2 (0.3 M in Et_2O) for 15 min at r.t. to afford a diastereomeric mixture of **21b** (94 mg, 95 %). Separation was accomplished by flash chromatography (silica gel, EtOAc /*n*-hexane = 1/2). *Less polar diastereomer*: ^{1}H-NMR: δ 1.87-3.24 (m, 8H, H_1, H_2, H_4, H_5, C_2-CH_2), 3.51 (s, 3H, OMe), 7.02-7.33 (m, 5H, Ph); IR (CCl_4): ν 1740 (C=O, ketone), 1435, 1260, 700 cm^{-1}; CapGC/EI/MS: m/e 232 (M^+), 201 (M-OMe), 173 (M-COOMe), 91; *More polar diastereomer*: ^{1}H-NMR: δ 1.96-2.22 (m, 2H), 2.31-2.71 (m, 4H), 3.02-3.40 (m, 2H, H_1, H_2, H_4, H_5, C_2-CH_2), 3.69 (s, 3H, OMe), 7.04-7.28 (m, 5H, Ph); IR (CCl_4): ν 1745 (C=O, ketone), 1370 cm^{-1}; CapGC/EI/MS: m/e 232 (M^+), 201, 173 (M-COOMe), 145 (M-COOMe-CO), 91; Found 232.1108. $C_{14}H_{16}O_3$ requires 232.1099.

Methyl 2-benzyl-5-methyl-3-oxocyclopentane carboxylate **21e**

A soln of **20e** (187 mg, 0.806 mmol) in CH_2Cl_2 was reacted with CH_2N_2 (0.3 M in Et_2O) at r.t. for 15 min to afford a diastereomeric mixture of **21e** (174 mg, 88 %). Attempts to separate these diastereomers by flash chromatography were unsuccessful. CapGC/MS showed that all diastereomers had almost identical mass spectra. IR (CCl_4): ν 2960, 1740 (C=O) cm^{-1}; EI/MS: m/e 246 (M^+), 187 (M-COOMe), 91.

Methyl 2-benzyl-5-n-butyl-3-oxocyclopentane carboxylate **21f**

A soln of **20f** (90 mg, 0.328 mmol) in CH_2Cl_2 was treated with CH_2N_2 (0.3 M in Et_2O) at r.t. for 15 min to afford a diastereomeric mixture of **21f** (95 mg, 100 %) in a ratio of 36:45:16 (CapGC). Attempts to separate these diastereomers by flash chromatography were unsuccessful. CapGC/MS showed that all diastereomers had almost identical mass spectra. ^{1}H-NMR: δ 0.73-0.98 (m, 3H, CH_3), 1.08-1.44 (m, 6H, C_4-$(CH_2)_3$), 2.06-3.40 (m, 7H, H_1, H_2, H_4, H_5, C_2-CH_2), 3.44, 3.61 and 3.71 (s,s,s, 3H, OMe, ratio = 25:74:60), 7.02-7.33 (m, 5H, Ph); IR (CCl_4): ν 2960, 2930, 1740 (C=O), 1200, 1170 cm^{-1}; EI/MS: m/e 288 (M^+); Found 288.1714. $C_{18}H_{24}O_3$ requires 288.1725.

FVT of **5a**

Epoxide **5a** (27 mg, 0.124 mmol) was subjected to FVT [sample temp.: 100 °C, oven temp.: 550 °C, p: 1.5.10^{-2} mm Hg, cold trap temp.: -196 °C] to produce crude **27a** (13 mg). The crude mixture was dissolved in hot *n*-hexane and insoluble impurities were removed by careful decantation. Subsequent evaporation of the solvent *in vacuo* gave NMR-pure **27a** (8 mg, 42 %) as a viscous oil. *2,7-Dioxo-3,8-dioxabicyclo*[4.3.0]*nona-*1(6),4-*diene* **27a**: ^{1}H-NMR: δ 5.23 (d, J=0.8 Hz, 2H, H_9), 6.68 (d, J=5.2 Hz, 1H, H_5), 7.68 (dd, J=5.2 Hz, J=0.8 Hz, 1H, H_4); IR (CCl_4): ν 1780 (C=O, lactone), 1750 (C=O, pyrone) cm^{-1}; EI/MS: m/e 152 (M^+); Found 152.0112. $C_7H_4O_4$ requires 152.0109.

Epoxide **5a** (26 mg, 0.12 mmol) was subjected to FVT [sample temp.: 100 °C, oven temp.: 500 °C, p: 1.5.10^{-2} mm Hg, cold trap temp.: -196 °C] to produce a mixture of **5a**, **25a** and **27a** in a molar ratio of 1:2:1 (^{1}H-NMR). **25a** was characterized by its ^{1}H-NMR spectral data. *2,6-Dioxo-7,8-epoxy-3-oxabicyclo*[3.3.0]*oct-*1(5)-*ene* **25a**: ^{1}H-NMR: δ 4.06 A of AB (d, ^{2}J=10 Hz, 1H, H_4), 4.36 B of AB (d, ^{2}J=10 Hz, 1H, H_4), 4.38 (d, J=3.2 Hz, 1H, H_7), 4.98 (d, J=3.2 Hz, 1H, H_8).

FVT of **5b**

Epoxide **5b** (51 mg, 0.173 mmol) was subjected to FVT [sample temp.: 120-140 °C, oven temp.: 520 °C, p: 1.5.10^{-2} mm Hg, cold trap temp.: -196 °C] to produce slowly a mixture of **27b** and three aldehydes (36 mg crude yield). Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3, Rf = 0.1) gave NMR-pure **27b** (11 mg, 28 %) as a sticky oil. *2,7-Dioxo-9-phenyl-3,8-dioxabicyclo*[4.3.0]*nona-*1(6),4-*diene* **27b**: ^{1}H-NMR: δ 6.37 (br s, 1H, H_9), 6.73 (d, J=5.2 Hz, 1H, H_5), 7.40 (s, 5H, Ph), 7.69 (dd, J=5.2 Hz, J=0.8 Hz, 1H, H_4); IR (CCl_4): ν 2925, 1788 (C=O, lactone), 1757 (C=O, pyrone), 1575 (C=C, unsat.) cm^{-1}; EI/MS: m/e 228 (M^+), 200 (M-CO), 199, 172 (M-2CO), 105 ($PhCO^+$), 77; Found 228.0422. $C_{13}H_8O_4$ requires 228.0423.

FVT of **5c**

Epoxide **5c** (31 mg, 0.113 mmol) was subjected to FVT [sample temp.: 115-125 °C, oven temp.: 580 °C, p: 1.5.10^{-2} mm Hg, cold trap temp.: -196 °C] to produce slowly crude **27c** (21 mg). Flash chromatography gave pure **27c** (12 mg, 51 %) as a white solid. 9-t-*Butyl-2,7-dioxo-3,8-dioxabicyclo*[4.3.0]*nona-*1(6),4-*diene* **27c**: m.p. 128-130 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ

1 10 (s, 9H, *t*-Bu), 5 19 (d, J=0 9 Hz, 1H, H_9), 6 65 (d, J=5 1 Hz, 1H, H_5), 7 68 (dd, J=5 1 Hz, J=0 9 Hz, 1H, H_4), IR (KBr) ν 2960, 1755 (C=O, lactone), 1728 (C=O, pyrone), 1577 (C=C, unsat), 1250 cm $^{-1}$, CI/MS m/e 209 (M^++1), UV (MeOH) λ_{max} 311 nm (9000), Found C, 63 82, H, 5 78 $C_{11}H_{12}O_4$ requires C, 63 45, H, 5 81

Epoxide **25c** was formed in *ca* 10 % crude yield (^{1}H-NMR) when oven temperatures between 450-550 °C were applied and was characterized by its ^{1}H NMR spectral data 4-t-*Butyl* 2,6 *dioxo*-7,8-*epoxy*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **25c** ^{1}H-NMR δ 1 10 (s, 9H, *t*-Bu), 4 09 (d, J=2 4 Hz, 1H, H_7), 4 36 (d, J=2 4 Hz, 1H, H_8), 4 76 (s, 1H, H_4)

FVT of **5d**

Epoxide **5d** (46 mg, 0 152 mmol) was subjected to FVT [sample temp 120 °C, oven temp 510 °C, p 2 10 $^{-2}$ mm Hg, cold trap temp -196 °C] to produce slowly crude **27d** (20 mg) Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1) gave NMR-pure **27d** (15 mg, 42 %) as a white solid *2,7-Dioxo* 9-n-*hexyl*-3,8-*dioxabicyclo*[4 3 0]*nona*-1(6),4-*diene* **27d** m p 80 82 °C (after recrystallization from *n* hexane) ^{1}H NMR δ 0 69-1 71 (m, 13H, *n*-hexyl), 5 26-5 49 (m, 1H, H_9), 6 65 (d, J=5 2 Hz, 1H, H_5), 7 66 (dd, J=5 2 Hz, J=0 6 Hz, 1H, H_4), IR (CCl_4) ν 1785 (C=O, lactone), 1747 (C=O, pyrone), 1575 (C=C, unsat) cm $^{-1}$, EI/MS m/e 236 (M^+), 192, 152 (M+1-C_6H_{13}), 124, 43, Found 236 1031 $C_{13}H_{16}O_4$ requires 236 1049

Epoxide **25d** was formed in *ca* 30 % crude yield (^{1}H-NMR) when oven temperatures between 400-500 °C were applied and was characterized by its ^{1}H-NMR spectral data 2,6-*Dioxo*-7,8-*epoxy*-4-n-*hexyl*-3-*oxabicyclo*[3 3 0]*oct* 1(5)-*ene* **25d** ^{1}H NMR δ 0 73-1 71 (m, 13H, *n*-hexyl), 4 09 (d, J=2 4 Hz, 1H, H_7), 4 33 (d, J=2 4 Hz, 1H, H_8), 5 22 (t, J=6 0 Hz, 1H, H_4)

FVT of **5e**

Epoxide **5e** (39 mg, 0 136 mmol) was subjected to FVT [sample temp 120 °C, oven temp 520 °C, p 2 10 $^{-2}$ mm Hg, cold trap temp -196 °C] to produce slowly crude **27e** (21 mg) Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3) gave NMR-pure **27e** (14 mg, 47 %) as a white solid *2,7 Dioxo* 3,8 *dioxabicyclo*[4 3 0]*nona*-1(6),4-*diene*-9-*spirocyclohexane* **27e** m p 140-142 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 1 10-2 49 (m, 10H, cyclohexyl), 6 63 (d, J=5 3 Hz, 1H, H_5), 7 64 (d, J=5 3 Hz, 1H, H_4), IR (CCl_4) ν 2935, 1780 (C=O, lactone), 1748 (C=O, pyrone), 1575 (C=C, unsat), 1170, 1100, 960 cm $^{-1}$, EI/MS m/e 220 (M^+), 192 (M CO), 164 (M-2CO), 136, 108, Found 220 0733 $C_{12}H_{12}O_4$ requires 220 0736

Epoxide **25e** was formed in *ca* 30 % crude yield (^{1}H-NMR) when an oven temp of 450 °C was applied and was characterized by its ^{1}H-NMR spectral data 2,6-*Dioxo*-7,8-*epoxy*-3-*oxabicyclo*-[3 3 0]*oct*-1(5) *ene* 4-*spirocyclohexane* **25e** ^{1}H-NMR δ 1 10-2 49 (m, 10H, cyclohexyl), 4 05 (d, J=2 3 Hz, 1H, H_7), 4 31 (d, J=2 3 Hz, 1H, H_8)

FVT of **5f**

Epoxide **5f** (35 mg, 0.142 mmol) was subjected to FVT [sample temp.: 100-110 °C, oven temp.: 510 °C, p: 2.10^{-2} mm Hg, cold trap temp.: -196 °C] to produce slowly crude **27f** (30 mg). Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1) gave NMR-pure **27f** (13 mg, 51 %) as a white solid, purity by CapGC 99.3 %. 9,9-*Dimethyl-2,7-dioxo*-3,8-*dioxabicyclo*[4.3.0]*nona*-1(6),4-*diene* **27f**: m.p. 129-131.5 °C (after recrystallization from *n*-hexane). ^{1}H-NMR: δ 1.70 (s, 6H, 2xC_9-Me), 6.63 (d, J=5.3 Hz, 1H, H_5), 7.65 (d, J=5.3 Hz, 1H, H_4); IR (CCl_4): ν 2980, 1778 (C=O, lactone), 1745 (C=O, pyrone), 1575 (C=C, unsat.), 1300, 1235, 1200 cm^{-1}; EI/MS: m/e 180 (M^+), 165 (M-CH_3), 138 (M-CH_3-CO), 123 (M-2CH_3-CO), 110 (M-CH_3-2CO), 95 (M-2CH_3-2CO); Found 180.0429. $C_9H_8O_4$ requires 180.0423.

Epoxide **25f** was formed in *ca.* 30 % crude yield (^{1}H-NMR) when an oven temp. of 450 °C was applied and was characterized by its ^{1}H-NMR spectral data. 4,4-*Dimethyl*-2,6-*dioxo*-7,8-*epoxy*-3-*oxa-bicyclo*[3.3.0]*oct*-1(5)-*ene* **25f**: ^{1}H-NMR: δ 1.54 (s, 3H, C_4-Me), 1.59 (s, 3H, C_4-Me), 4.07 (d, J=2.3 Hz, 1H, H_7), 4.33 (d, J=2.3 Hz, 1H, H_8).

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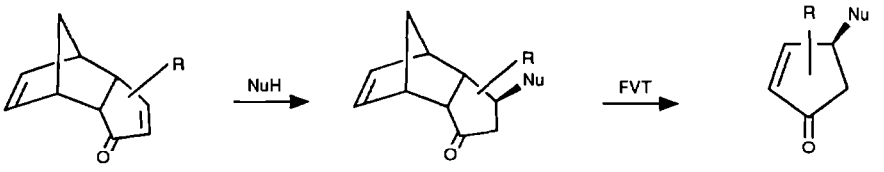
CHAPTER 5

AN EFFICIENT ENANTIOSELECTIVE SYNTHESIS OF LACTONE ANNELATED CYCLOPENTENOIDS FROM OPTICALLY ACTIVE ETHYL TRICYCLO[5.2.1.0^{2,6}]DECA-DIENONE 2-CARBOXYLATE

5.1 INTRODUCTION

The tricyclo[5.2.1.0^{2,6}]decadienone system **1** constitutes a versatile synthetic equivalent of cyclopentadienone. Chemical modification of the enone moiety in **1**, *e.g.* by nucleophilic addition, leads stereospecifically to **2**, which on flash vacuum thermolysis produces cyclopentenones **3** with a well-defined stereochemistry[1] (Scheme 1). Using this strategy, a variety of cyclopentenoids has been prepared (see Chapter 1).

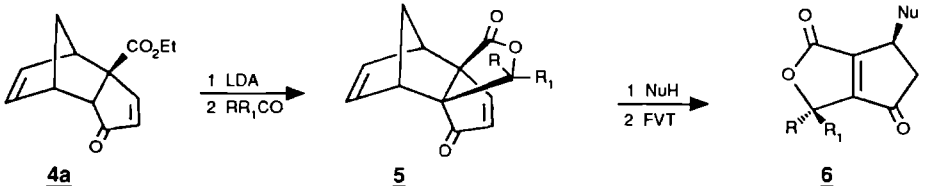
Scheme 1



1 **2** **3**

In Chapter 4 the stereoselective synthesis of bridged [4.3.3]oxapropellanes **5** by angular condensation of ethyl tricyclodecadienone carboxylate **4a** and their thermal conversion into γ-lactone annelated cyclopentenoids **6** was reported[2] (Scheme 2). These compounds **6** constitute unique structures as they contain a butenolide as well as a cyclopentenoid unit with a common double bond. By stereoselective reduction of this central double bond in **6**, using zinc in acetic acid, the synthesis of some analogues of the naturally occurring antitumor compound (±)-sarkomycin was accomplished.

Scheme 2



4a **5** **6**

The availability of a practical preparation of both antipodes of cyclopentenoids **6** would be very attractive from synthetic point of view. Optically active 5-substituted butenolides can serve as chirons in the synthesis of antibiotics[3], steroids[4] and antileukaemic lignans[5]. Most of these homochiral butenolides are prepared from optically active natural precursors, *e.g.* D-sugars[3,6] and L-amino acids[5]. A limitation of the approach, using a chiral pool, is that generally only one of the enantiomers is

accessible

The recent finding of an efficient enzymic optical resolution of tricyclic ester **4a** using pig's liver esterase (PLE) or maxatase, which gives access to both antipodes of the tricyclodecadienone system[7,8], was a stimulus to explore the synthesis of optically active **6** starting from these optically pure esters

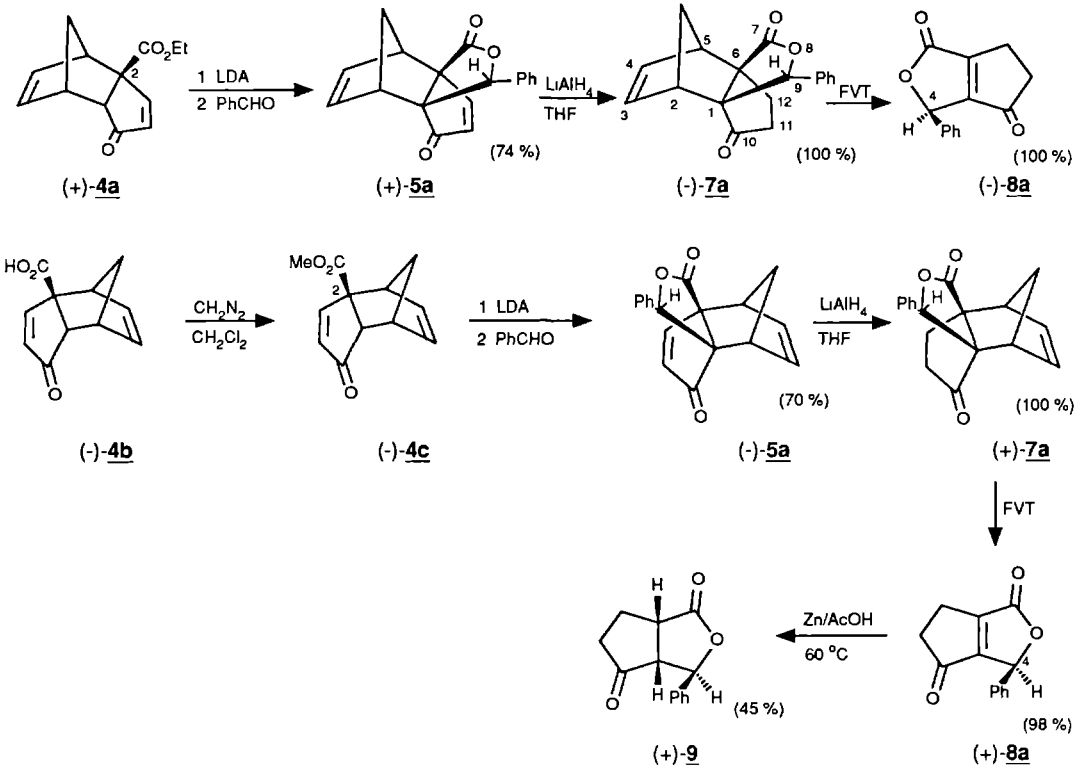
5.2 SYNTHESIS OF OPTICALLY PURE LACTONE ANNELATED CYCLOPENTENOIDS

In order to obtain an optically active cyclopentenoid **6**, this compound must at least contain one chiral center, which preferentially should be introduced stereospecifically at some stage of its synthesis. Therefore, the condensation of benzaldehyde with the enolate of optically pure ester (+)-**4a** was selected, because this reaction produces[2] stereospecifically 4-phenyl substituted tetracyclic lactone **5a**. Treatment of (+)-**4a** ($[\alpha]_D$ = 105.6°, MeOH, ee > 99 %) with LDA and quenching the enolate with benzaldehyde (see Chapter 3) gave (+)-tetracyclic 9-phenyl lactone **5a** ($[\alpha]_D$ = + 13.3°, $CHCl_3$) in 74 % yield (Scheme 3). Subsequent selective conjugate reduction employing $LiAlH_4$ at -78 °C for 5 min, quantitatively afforded (-)-lactone **7a** ($[\alpha]_D$ = - 53°, $CHCl_3$). Under these reductive conditions the lactone ring of **5a** as well as its C_{10} carbonyl group remain unaffected. The optical purity of **7a** could accurately be established using ^{1}H-NMR spectroscopy in combination with optically active Eu(III)-$(hfc)_3$ shift reagent. With racemic **7a** complete separation of the H_9 signal, as well as the ortho/para proton absorptions of its C_9-phenyl group, was observed in the formed diastereomeric Eu-complex. This enabled an unambiguous establishment of its enantiomeric excess (ee) which was found to be greater than 98 %. Flash vacuum thermolysis of (-)-**7a** afforded the desired optically active annelated cyclopentenoid butenolide (-)-**8a** ($[\alpha]_D$ = - 19.6°, $CHCl_3$).

Unfortunately, the optical purity of **8a** could not unequivocally be established by spectroscopic means. However, the observation that the thermal cycloreversion of racemic tetracyclic lactones **7** containing chirality at both C_9 and C_{12} proceeds without any epimerization (see Section 4.2) indicates that no racemization is to be expected during the thermal cycloreversion of (-)-**7a** either. Hence, the optical purity of cyclopentenoid (-)-**8a** is assumed to be the same as that of the starting propellane (-)-**7a**. In order to add more evidence, the antipode of (-) **8a** was also prepared. Therefore, (-)-acid **4b** was esterified by reaction with diazomethane to yield (-)-methyl ester **4c** in 92 % yield. The same route as described above, but now starting from (-)-methyl ester **4c** ($[\alpha]_D$ = - 83.3°, MeOH) which had a slightly lower optical purity (ee of 88 %) yielded (-)-9-phenyl-8-oxa[4.3.3]propellane **5a** ($[\alpha]_D$ = - 13.3°, $CHCl_3$) in 72 % yield (Scheme 3). As the last mentioned compound had the same optical rotation but with an opposite sign, in comparison with its (+)-enantiomer **5a** (that had been obtained from optically pure (+)-**4a**), optical enrichment must have taken place during the recrystallization of (-)-**5a**. This was confirmed by the observation of a low optical rotation ($[\alpha]_D$ = - 2.8°, $CHCl_3$) for **5a** after purification of the remaining mother liquor by flash chromatography and subsequent recrystallization. Conjugate reduction of ( ) **5a** with $LiAlH_4$ produced (+)-lactone **7a** ($[\alpha]_D$ = + 54°, $CHCl_3$) in quanti-

tative yield. Flash vacuum thermolysis finally gave (+)-**8a** ($[\alpha]_D$ = + 19.1°; $CHCl_3$) in almost quantitative yield. The close agreement of the optical rotations for all pairs of (+)- and (-)-enantiomers of the newly prepared compounds proves the chiral integrity during both reaction sequences.

Scheme 3



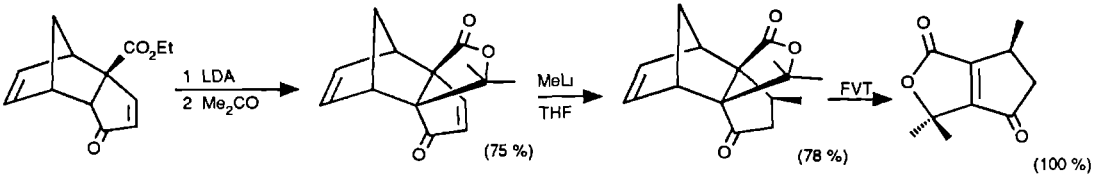
The absolute configurations of both antipodes (-)-**8a** and (+)-**8a**, which is (R) and (S) at C_4, respectively, can be readily derived from the known absolute configurations[7] of tricyclic esters (+)-**4a** and (-)-**4c**. In Scheme 3 the absolute configurations of esters (+)-**4a**, (-)-**4c** and their reaction products are pictured.

The selective reduction of (+)-**8a** ($[\alpha]_D$ = + 15.8°; $CHCl_3$, ee of 81 %) with Zn-dust in acetic acid was carried out at 60 °C and afforded 4-phenyl-cyclosarkomycin (+)-**9** ($[\alpha]_D$ = + 111°; $CHCl_3$) in 45 % yield, after flash chromatographic purification. Repeating this experiment, but now starting from optically pure (+)-**8a** ($[\alpha]_D$ = + 19.6°; $CHCl_3$) gave (+)-**9** ($[\alpha]_D$ = + 165°; $CHCl_3$) in 45 % yield as a NMR-pure oil. Comparison of both results reveals that the optical integrity during the selective reduction process is questionable. The optical purities of (+)-**9a** in both reactions were not determined. The loss of stereochemical integrity in the aforementioned reductive process can be readily explained by the occurrence of partial epimerization at the benzylic C_4-atom of (+)-**8a** in the acidic reaction

medium[9] (see Scheme 2 in Chapter 4).

In order to illustrate the generality of this route to optically active cyclopentenoids **8**, optically pure substituted oxapropellane (+)-**7b** was prepared and its thermal cycloreversion was investigated. Although studies with racemic **7**, containing chiral centers at both C_9 and C_{12}, already indicated that no epimerization occurs during the thermal cycloreversion step, these investigations with homochiral material would definitely exclude such possibility. Optically pure (+)-ester **4a** ($[\alpha]_D$ = + 105.6°; MeOH) was condensed with acetone to furnish (+)-lactone **5b** ($[\alpha]_D$ = + 188°; $CHCl_3$) in excellent yield (Scheme 4). Stereospecific conjugate methylation employing MeLi at -78 °C in THF gave 12-*anti*-methylated (+)-lactone **7b** ($[\alpha]_D$ = + 4.9°; $CHCl_3$) in 78 % yield.

Scheme 4



The enantiomeric excess of (+)-**7b** was again established by ^{1}H-NMR spectroscopy and homochiral Eu(III)(hfc)$_3$ shift reagent. It appeared to be greater than 98 %. This optically pure (+)-12-methyl-8-oxa[4.3.3]propellane **7b** was now subjected to FVT (520 °C, p = 10^{-2} torr) to furnish (-)-(S)-butenolide **8b** ($[\alpha]_D$ = - 21.7°; $CHCl_3$) in almost quantitative yield. ^{1}H-NMR shift experiments revealed **8b** to have an enantiomeric excess greater than 98 %, thus demonstrating again the chiral integrity in the thermal cycloreversion reaction.

In conclusion, an efficient synthesis of some representative optically pure lactone annelated cyclopentenones **8** was accomplished, starting from readily available homochiral tricyclic esters **4**.

5.3 EXPERIMENTAL PART

General

The remarks given in Section 2.5 also apply here. Optical rotations were determined by using a Perkin Elmer 241 polarimeter. The optical purities of the compounds were determined with tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III)-derivative (Eu(III)(hfc)$_3$) as homochiral NMR shift reagent.

Syntheses

*Kinetic enzymic resolution of (±)-**4a***

To a stirred Na/K-phosphate buffer soln (0.1 M, pH=8, 650 ml) was successively added CH_3CN (7 ml), maxatase enzyme (5.0 g)[10] and (±)-**4a** (11.9 g, 54.6 mmol) at r.t. The pH was kept constant at pH=8 by addition of 0.2 N NaOH during the reaction using an auto-titrator. The reaction was stopped after 30 h by addition of Na_2CO_3 aq until pH 10.7 was reached. The reaction mixture was then carefully extracted with Et_2O (4x), the organic layer washed, dried ($MgSO_4$) and evaporated *in vacuo*, to yield crude (+)-**4a** (5.72 g). Recrystallization twice from *n*-pentane afforded optically pure (+)-**4a** (3.73 g, 31 %). (+)-(1R,2S,6R,7S)-*Ethyl 5-oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene 2-carboxylate* **4a**: m.p. 35-37 °C (lit.[8] 35-37 °C); $[\alpha]_D^{25}$= + 105.6° (c = 0.5; MeOH) (ee > 99 %[8]). After acidification of the remaining aqueous layer to pH=1 with HCl (20 % aq), careful extraction with Et_2O (3x), drying ($MgSO_4$) and evaporation *in vacuo*, (-)-acid **4b** (3.25 g, 31 %) was obtained as a white solid. (-)-(1S,2R,6S,7R)-5-*Oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene 2-carboxylic acid* **4b**: m.p. 122-128 °C (lit.[7] 125-130 °C for optically pure (-)-**4b**): $[\alpha]_D^{25}$= - 76° (c = 0.22; MeOH) (ee 90 %[7]).

(-)-(1S,2R,6S,7R)-*Methyl 5-oxo*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*deca*-3,8-*diene 2-carboxylate* **4c**

(-)-Acid **4b** (3.2 g, 16.8 mmol, ee 90 %) was stirred with CH_2N_2 (56 ml, 0.3 M soln in Et_2O, 16.8 mmol) in 20 ml of CH_2Cl_2 at r.t. for 15 min to afford (-)-**4c** (3.15 g, 92 %) as a white solid after flash chromatography (Silica, ethyl acetate /*n*-hexane = 1/1, Rf = 0.5); m.p. 65-68 °C (lit.[7] 67-68 °C); $[\alpha]_D^{25}$= - 83.3° (c = 0.19; MeOH) (ee[7] 88 %).

(+)-(1R,2S,5R,6S,9R)-7,10-*Dioxo*-9-*phenyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*trideca*-3,11-*diene* **5a**

The procedure was the same as described for the synthesis of racemic lactone **5a** (Section 3.7). Using (+)-**4a** (1.18 g, 5.41 mmol, $[\alpha]_D^{25}$= + 105.6° (c = 0.5; MeOH)), *n*-BuLi (4.1 ml, 1.6 M in *n*-hexane, 6.56 mmol), diisopropylamine (0.547 g, 5.42 mmol) and benzaldehyde (0.688 g, 6.49 mmol) furnished NMR-pure (+)-**5a** (1.12 g, 74 %). Excess of benzaldehyde was removed by extraction with hot *n*-hexane (3x). Recrystallization from ethyl acetate /*n*-hexane (1/3) gave analytically pure (+)-**5a**. m.p. 172-174 °C (dec.); $[\alpha]_D^{25}$= + 13.3° (c = 0.96; $CHCl_3$). The spectral data were identical with those of (±)-**5a**. Found C, 77.51; H, 5.16. $C_{18}H_{14}O_3$ requires C, 77.68; H, 5.07. Attempts to determine the enantiomeric excess of (+)-**5a** with Eu(III)$(hfc)_3$ were unsuccessful.

(-)-(1S,2R,5S,6R,9S)-7,10-*Dioxo*-9-*phenyl*-8-*oxatetracyclo*[4.3.3.$1^{2,5}$.$0^{1,6}$]*trideca*-3,11-*diene* **5a**

The procedure was the same as previously described for the synthesis of racemic **5a** (Section 3.7). Using (-)-**4c** (3.17 g, 15.5 mmol, $[\alpha]_D^{25}$= - 83.3° (c = 0.19; MeOH)), *n*-BuLi (12.6 ml, 1.6 M in *n*-hexane, 20.2 mmol), diisopropylamine (1.89 g, 18.7 mmol) and benzaldehyde (2.14 g, 20.2 mmol) furnished NMR-pure (-)-**5a** (3.01 g, 70 %). Excess of benzaldehyde was removed by extraction with hot *n*-hexane (3x). Recrystallization from ethyl acetate /*n*-hexane (1/3) gave analytically pure (-)-**5a**.

m.p. 165 °C (dec. with concomitant sublimation >130 °C); $[\alpha]_D^{25}$= - 13.3° (c = 0.79; $CHCl_3$). The spectral data were identical with those of (±)-**5a**. Found C, 77.50; H, 5.06. $C_{18}H_{14}O_3$ requires C, 77.68; H, 5.07. Attempts to determine the enantiomeric excess of (-)-**5a** with Eu(III)(hfc)$_3$ were unsuccessful.

(+)-(1S,2R,5S,6S,9S)-7,10-*Dioxo*-9-*phenyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **7a**

The procedure was the same as described previously for the synthesis of racemic **7a** (Section 3.7). Using (-)-**5a** (1.94 g, 6.98 mmol, $[\alpha]_D^{25}$= - 13.3° (c = 0.79; $CHCl_3$)), $LiAlH_4$ (0.31 g, 8.16 mmol) in THF (20 ml), furnished NMR-pure (+)-**7a** (1.95 g, 100 %). Recrystallization from *n*-hexane gave analytically and optically pure (+)-**7a**. m.p. 160-164 °C (dec. with concomitant sublimation >150 °C); $[\alpha]_D^{25}$= + 54° (c = 1.25; $CHCl_3$, ee > 98 %). The spectral data were identical with those of (±)-**7a**. Found C, 76.64; H, 5.78. $C_{18}H_{16}O_3$ requires C, 77.12; H, 5.75. After addition of a fivefold molar excess of Eu(III)(hfc)$_3$ both the signals of H_9 and those of the phenylic ortho protons in racemic **7a** were completely split. (+)-**7a** was shown to be optically pure by addition of Eu(III)(hfc)$_3$ as the shift reagent.

(-)-(1R,2S,5R,6R,9R)-7,10-*Dioxo*-9-*phenyl*-8-*oxatetracyclo*[4.3.3.1^{2,5}.0^{1,6}]*tridec*-3-*ene* **7a**

The procedure was the same as described previously for the synthesis of racemic **7a** (Section 3.7). Using (+)-**5a** (0.900 g, 3.24 mmol, $[\alpha]_D^{25}$= + 13.3° (c = 0.96; $CHCl_3$)), $LiAlH_4$ (0.15 g, 3.94 mmol) in THF (10 ml), furnished NMR-pure (-)-**7a** (0.91 g, 100 %). Recrystallization from *n*-hexane gave analytically pure (-)-**7a**. m.p. 155 °C (dec.); $[\alpha]_D^{25}$= - 53° (c = 1.18; $CHCl_3$, ee > 98 %). The spectral data were identical with those of (±)-**7a**. Found C, 77.00; H, 5.83. $C_{18}H_{16}O_3$ requires C, 77.12; H, 5.75.

(+)-(4S)-2,6-*Dioxo*-4-*phenyl*-3-*oxabicyclo*[3.3.0]*oct*-1(5)-*ene* **8a**

The same FVT procedure as described for the synthesis of racemic **8a** was applied (Section 4.6). Using (+)-**7a** (0.95 g, 3.39 mmol, $[\alpha]_D^{25}$= + 54° (c = 1.25; $CHCl_3$)) gave crude white-yellow (+)-**8a** (0.713 g, 98 %). Recrystallization from ethyl acetate /*n*-hexane (1/3) gave analytically pure (+)-**8a** as a white solid. m.p. 129-136 °C; $[\alpha]_D^{25}$= + 19.6° (c = 1.31; $CHCl_3$). The spectral data were identical with those of (±)-**8a**. Found C, 73.64; H, 4.81. $C_{13}H_{10}O_3$ requires C, 72.89; H, 4.71. Attempts to determine the enantiomeric excess of (+)-**8a** with Eu(III)(hfc)$_3$ were unsuccessful.

(-)-(4R)-2,6-*Dioxo*-4-*phenyl*-3-*oxabicyclo*[3.3.0]*oct*-1(5)-*ene* **8a**

The same FVT procedure as described for the synthesis of racemic **8a** was applied (Section 4.6). Using (-)-**7a** (0.350 g, 1.25 mmol, $[\alpha]_D^{25}$= - 53° (c = 1.18; $CHCl_3$)) gave crude white-yellow (-)-**8a** (0.280 g, 100 %). Recrystallization from ethyl acetate /*n*-hexane (1/3) gave analytically pure (-)-**8a** as a white solid. m.p. 134-136 °C; $[\alpha]_D^{25}$= - 19.1° (c = 0.47; $CHCl_3$). The spectral data were identical with those of (±)-**8a**. Found C, 73.00; H, 4.75. $C_{13}H_{10}O_3$ requires C, 72.89; H, 4.71. Attempts to deter-

mine the enantiomeric excess of (-)-**8a** with Eu(III)(hfc)$_3$ were unsuccessful

(+)-(1S,4R,5R)-2,6-*Dioxo*-exo-4-*phenyl*-cis-3-*oxabicyclo*[3 3 0]*octane* **9**

Zn dust (600 mg, 9 18 mmol), (+)-**8a** (480 mg, 2 24 mmol, $[\alpha]_D^{25}$= + 19 6° (c = 1 31, $CHCl_3$)) and AcOH (15 ml) were reacted as described previously (Chapter 4) for the reduction of racemic **8a** to yield (+)-**9** (216 g, 45 %) as a pure oil after flash chromatography $[\alpha]_D^{25}$= + 165° (c = 0 68, $CHCl_3$) The spectral data were identical with those of (±)-**9** Repeating this experiment with (+)-**8a** ($[\alpha]_D^{25}$= + 15 8° (c = 0 594, $CHCl_3$), ee 81 %) gave pure (+)-**9** (110 mg, 45 %, $[\alpha]_D^{25}$= + 111° (c = 0 25, $CHCl_3$)) after flash chromatography In both cases the enantiomeric excess was not determined

(+)-(1R,2S,5R,6S)-9,9-*Dimethyl*-7,10-*dioxo*-8-*oxatetracyclo*[4 3 3 $1^{2,5}$ $0^{1\ 6}$]*trideca*-3,11-*diene* **5b**

The procedure was the same as described previously for the synthesis of racemic **5b** (Section 3 7) Using (+)-**4a** (2 28 g, 10 46 mmol, $[\alpha]_D^{25}$= + 105 6° (c = 0 5, MeOH)), *n*-BuLi (7 85 ml, 1 6 M in *n*-hexane, 12 6 mmol), diisopropylamine (1 27 g, 12 6 mmol) and acetone (0 8 g, 13 8 mmol) afforded NMR-pure (+)-**5b** (1 8 g, 75 %) after flash chromatography (Silica, ethyl acetate /*n*-hexane (1/3), Rf = 0 3) Recrystallization from *n*-hexane /CH_2Cl_2 (20/1) gave analytically pure (+)-**5b** as a white solid m p 142-153 °C, $[\alpha]_D^{25}$= + 188° (c = 0 43, $CHCl_3$, ee > 95 %) The spectral data were identical with those of (±)-**5b** Found C, 72 88, H, 6 20 $C_{14}H_{14}O_3$ requires C, 73 03, H, 6 13 After addition of a twofold molar excess of Eu(III)(hfc)$_3$ the fastest downfield shifting C_9-CH_3 singlet in racemic **5b** was almost completely split (+)-**5b** was shown to be optically pure by means of Eu(III)(hfc)$_3$

(+)-(1R,2S,5R,6R,12S)-7,10-*Dioxo*-9,9,12-*trimethyl*-8-*oxatetracyclo*[4 3 3 $1^{2\ 5}$ $0^{2\ 6}$]*tridec*-3-*ene* **7b**

The procedure was the same as described previously for the synthesis of racemic **7b** (Section 3 7) Using (+)-**5b** (0 80 g, 3 48 mmol, $[\alpha]_D^{25}$= + 188° (c = 0 43, MeOH)) and MeLi (3 11 ml, 1 6 M in Et_2O, 4 98 mmol) in THF (15 ml) furnished NMR-pure (+)-**7b** (0 670 g, 78 %) after flash chromatography (Silica, ethyl acetate /*n*-hexane (1/2), Rf = 0 3, I_2) Recrystallization from *n*-hexane gave analytically pure (+)-**7b** m p 127-140 °C, $[\alpha]_D^{25}$= + 4 9° (c = 0 56, $CHCl_3$, ee > 98 %) The spectral data were identical with those of (±)-**7b** Found C, 72 83, H, 7 41 $C_{15}H_{18}O_3$ requires C, 73 15, H, 7 37 After addition of a twofold molar excess of Eu(III)(hfc)$_3$ both the fastest downfield shifting olefinic multiplet (derived from H_3 or H_4) and the doublet derived from H_{12} in racemic **7b** were completely split (+)-**7b** was shown to be optically pure by means of Eu(III)(hfc)$_3$

(-)-(8S)-2,6-*Dioxo*-4,4,8-*trimethyl*-3-*oxabicyclo*[3 3 0]*oct*-1(5)-*ene* **8b**

The same FVT procedure as described for the synthesis of racemic **8b** was applied (Section 4 6) Using (+) **7b** (0 190 g, 0 772 mmol, $[\alpha]_D^{25}$= + 4 9° (c = 0 56, $CHCl_3$)) afforded crude white-yellow (-)-**8b** (0 140 g, 100 %) Recrystallization from *n* hexane gave analytically pure (-)-**8b** as a white solid m p 70-73 °C, $[\alpha]_D^{25}$= - 21 7° (c = 0 62, $CHCl_3$, ee > 95 %) The spectral data were identical with those of (±)-**8b** Found C, 66 55, H, 6 72 $C_{10}H_{12}O_3$ requires C, 66 65, H, 6 71 After addition of

a sevenfold molar excess of Eu(III)(hfc)$_3$ the C_8-CH_3 doublet in racemic **8b** was almost completely split. (-)-**8b** was shown to be optically pure by means of Eu(III)(hfc)$_3$ mediated ^{1}H-NMR spectra.

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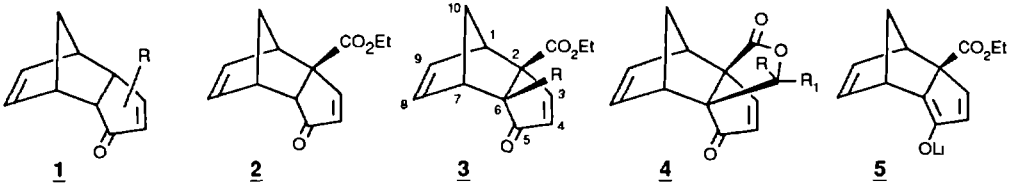
CHAPTER 6

SYNTHESIS AND REACTIONS OF EPOXYTRICYCLO[5.2.1.$0^{2,6}$]DECENOLS

6.1 INTRODUCTION

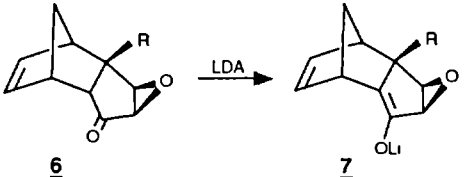
Tricyclo[5.2.1.$0^{2,6}$]decadienones **1** are useful synthetic equivalents of cyclopentadienones and serve as such as synthons for cyclopentanoid natural products[1]. Stereocontrolled conjugate addition to the cyclopentenone moiety together with appropriate functional group transformations, followed by a thermal [4+2] cycloreversion, using the flash vacuum thermolysis technique, allows the stereo- and enantioselective synthesis of a variety of cyclopentenoids in excellent chemical and optical yields[2]. Based on this strategy, the total synthesis of (±)-terrein[3], (±)-pentenomycin[4], (±)-sarkomycin and some of their derivatives has been accomplished. Access to the *endo*-tricyclodecadienone system is



1 **2** **3** **4** **5**

most conveniently acquired *via* ester **2**, which in turn can readily be obtained, racemic[5] as well as optically active[6], from cyclopentadiene and benzoquinone. In some recent papers, the angular functionalization of **2** by alkylation or condensation with appropriate electrophiles affording 6-alkyltricyclodecadienone esters **3** and bridged oxapropellanes **4**, respectively, was described[7,8]. In these angular functionalizations effective use is made of the anti-Bredt enolate **5**. While esters **3** appeared to be suitable precursors for 2-alkyl-3-carboethoxycyclopentadienones[9] and dihydrosarkomycins (Chapter 2), the tetracyclic lactones **4** gave access to sarkomycins (Chapter 4).

Scheme 1



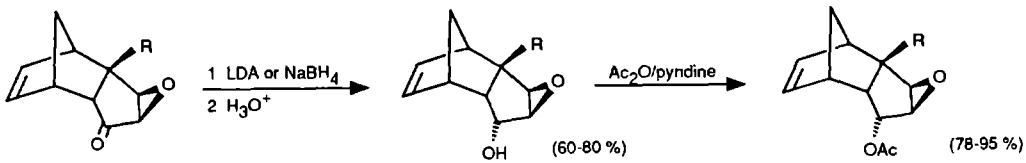
6 **7**

An interesting epoxide **6** was obtained from the tricyclo[5.2.1.$0^{2,6}$]dienones **1** by selective epoxidation of the enone function, using hydrogen peroxide in alkaline medium[3]. These epoxides are interesting substrates for a synthetic study, *e.g.* deprotonation to an anti-Bredt enolate analogous to **5** and selective reactions of either the epoxide or the carbonyl functions. In this Chapter particular attention will be given to the synthesis of the alcohols that can be derived from epoxy-tricyclodecenones **6**.

6.2 AN UNEXPECTED HYDRIDE TRANSFER IN THE REACTION OF 4,5-EPOXYTRICYCLO[5.2.1.$0^{2,6}$]DECENONES WITH LDA

With the aim to prepare the anti-Bredt enolate 7 (Scheme 1), epoxide **6b** was treated with LDA as a non-nucleophilic strong base similarly as enolate 5 has been obtained from enone 2. Reaction of **6b** with LDA at -78 °C in THF and subsequent quenching with methyl iodide did not produce the expected angular 6-methyl derivative of **6b**, but instead the reduced product **8b** (yield 80 %). The same product was obtained when water was used as the trapping agent instead of MeI (Scheme 2). Alcohol **8b** was also obtained from ester **6b** by reduction with $NaBH_4$, strongly suggesting that the stereochemistry of the alcohol function at C_5 is *endo*.

Scheme 2

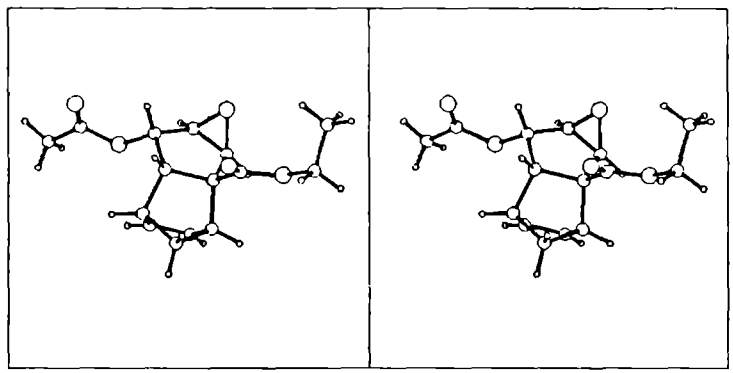


6 **8** **9**

a R=H, **b** R=CO_2Et

In order to firmly establish the structure of **8b**, it was acylated with acetic anhydride in pyridine, and the resulting crystalline acetate **9b** was subjected to an X-ray diffraction analysis[10]. This analysis indeed confirmed structure **8b** to possess the *endo*-configuration for the alcohol function at C_5 (Fig. 1).

Fig. 1

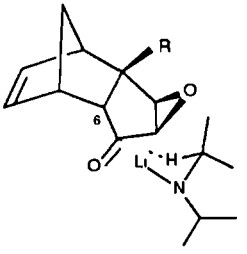


Parent tricyclic epoxide **6a** was also treated with LDA under the same conditions. Again, the starting epoxide had completely been consumed to give alcohol **8a** as the only identifiable product in a yield of 60 %. Although the somewhat lower yield obtained here, as compared with **6b**, may suggest that some deprotonation may have taken place to form enolate 7, no indications for products derived

from such an enolate were found in the ^{1}H-NMR spectrum of the crude reaction mixture It may therefore be concluded that the deprotonation of epoxides **6** using LDA does not lead to the formation of substantial amounts of epoxy enolates **7** Instead, a reduction of the C_5 ketone function in **6** takes place As no such reduction is observed for enone ester **2**, the presence of the *exo*-3,4-epoxide function apparently plays a crucial role in this reaction of **6** with LDA

Mechanistically, the stereoselective formation of **8** in the reaction of epoxyketones **6** with LDA can be rationalized by invoking a stereospecific hydride shift from one of the isopropyl groups of LDA to the carbonyl group of **6** (Fig 2)

Fig 2



a R=H **b** R=CO_2Et

Such a hydride transfer, which has been reported for aromatic ketones without enolizable α-hydrogens[11] and for some enolizable α-halo- and alkoxy ketones[12], is expected to take place selectively to the *convex* side of **6** *Endo*-alcohol **8** is produced as the sole product as the rigid *endo*-configuration of the tricyclic skeleton of **6** prevents attack at its *concave* side The reason for this exceptional behavior of LDA is most probably of steric origin Due to the bulkiness of LDA, abstraction of the C_6 hydrogen atom in **6** is particularly hampered by the *exo*-epoxide moiety which is positioned *syn* with respect to H_6 In the case of **6b** the ethoxycarbonyl group at C_2 enhances this steric hindrance of the approach of H_6 As a consequence, the reductive pathway becomes favorable

The angular deprotonation of **6** with LDA diverts because of the preferential occurrence of a β-hydride transfer to the ketone function, therefore this deprotonation of **6** was attempted with N-lithium-2,2,6,6-tetramethylpiperidine[13] (LTMP), a similar strong base as LDA, but lacking the ability for β-hydride transfer Again, no deprotonation was observed under a variety of conditions Quenching with electrophiles and nucleophiles such as MeI, D_2O and MeLi, did not afford any product that would indicate the formation of enolate **7** from **6** on treatment with LTMP As expected with this base, reduction of **6** had not taken place either The failure of both LDA and LTMP to deprotonate **6** convincingly demonstrates the inaccessibility of the angular proton H_6 in epoxy ketones **6**

The epoxy enolate **7** is thermodynamically probably significantly less stable than enolate **5**, as in the latter case there is considerable conjugative stabilization by the C_3-C_4 olefinic bond Moreover, it is likely that the strain energy of **7** is higher than that of **5** due to the epoxide annelation Although this decreased stabilization of enolate **7** will lead to a reduced acidity of the H_6 proton in **6**, it is unlikely

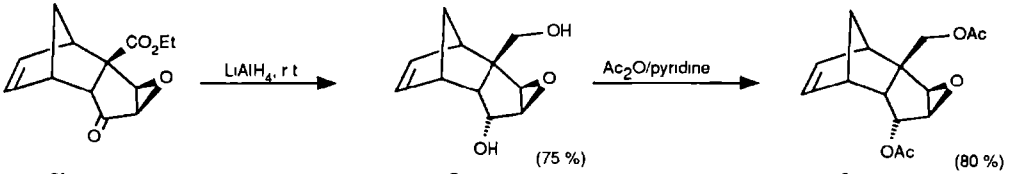
that the difference in pK_a value of the compounds **2** and **6** is decisive for the observed failure of **6** to form the anti-Bredt[14] enolate **7** when applying strong bases such as LDA and LTMP[13].

6.3 FLASH VACUUM THERMOLYSIS OF EPOXYTRICYCLODECENOLS AND THEIR ACETATES

The unexpected formation of *endo*-alcohols **8a** and **8b** from the reaction of **6a** and **6b** with LDA was a stimulus to investigate the thermal cycloreversion of these alcohols **8** and their acetates **9** in order to compare their thermal behavior with that of the corresponding tricyclic epoxy ketones **6**. In this context it is of interest to subject also the diacetate of the reduction product **8c** (Scheme 3) to a thermolysis.

The synthesis of **8c** was readily accomplished by reduction of ester **6b** with lithium aluminium hydride; subsequent acylation with acetic anhydride in pyridine gave diacetate **9c** in an overall yield of *ca.* 60 % based on **6b**.

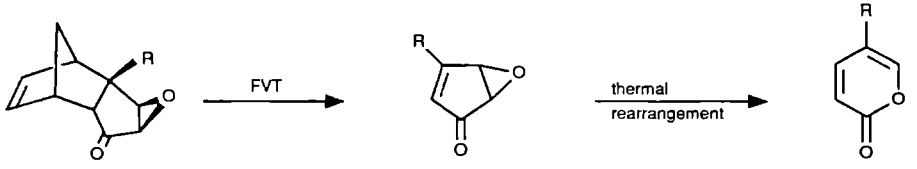
Scheme 3



6b **8c** **9c**

In previous papers[3,15] it was demonstrated that tricyclic epoxides **6** are precursors for the preparation of cyclopentadienone oxides **10** (Scheme 4). The synthetic accessibility of **10** depends strongly on the presence of a π-containing substituent at the angular position in **6**, enhancing the thermal stability of these cyclopentadienone oxides by extending the conjugation of its cyclic enone system. When

Scheme 4



6 **10** **11**

a R=H, **b** R=CO_2Et

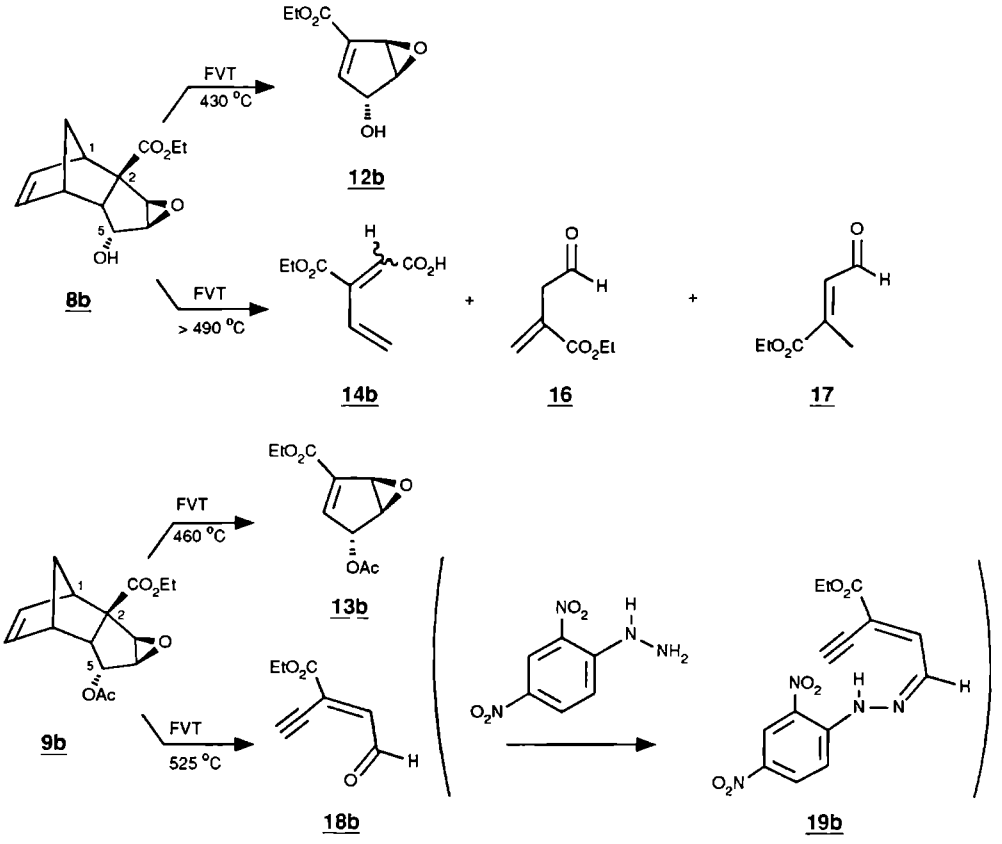
such an extended π-system is lacking, the cyclopentadienone oxides **10** rapidly rearrange to the corresponding α-pyrones **11** under the conditions of thermal cycloreversion of **6**. Accordingly, tricyclic ester **6b** afforded cyclopentadienone oxide **10b** in 55 % yield, while **6a** only led to the corresponding α-pyrone **11** upon flash vacuum thermolysis (FVT) (430 °C, 10^{-2} torr). The corresponding dimethyl acetals of **6** gave similar results[15], indicating that the presence of a ketone function is not required for the pre-

vention of a further thermal rearrangement

The behavior of compounds **6** during the thermal cycloreversion suggests that the tricyclic alcohols **8** and their acetates **9** will follow the same pattern on thermolysis and afford epoxycyclopentenols, particularly in those cases where there is a π-containing substituent at the γ-position.

In agreement with this prediction, epoxytricyclodecenol **8b** which contains an ester function at C_2, afforded epoxycyclopentenol **12b** when subjected to flash vacuum thermolysis at 420 °C (10^{-2} torr) (Scheme 5) Under these optimum conditions, no thermal rearrangement products derived from **12b** were formed, but also no complete conversion of the starting material could be reached Bulb to bulb distillation allowed separation of product and starting material, to give NMR-pure **12b** in a yield of 47 % In a similar way, acetate **9b** gave the corresponding epoxycyclopentene acetate **13b** in 47 % yield after bulb to bulb distillation (Scheme 5) Epoxycyclopentenol **12b** and its acetate **13b** were charac-

Scheme 5

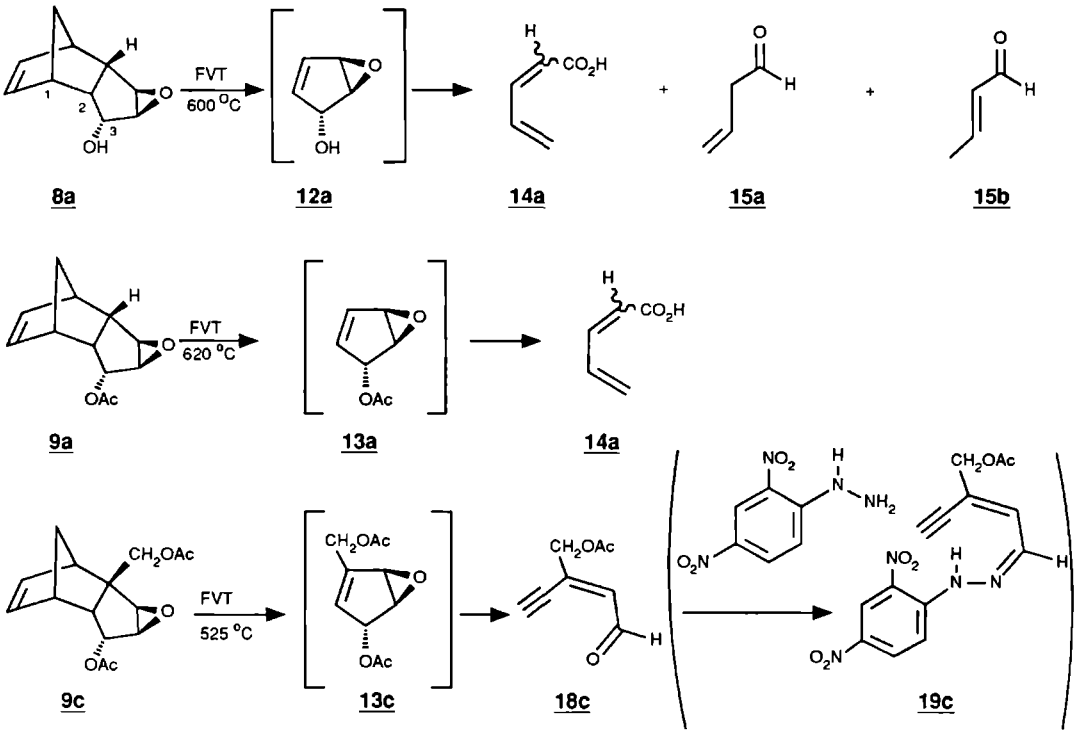


terized by their ^{1}H-NMR spectra Typically, acetate **13b** displays its olefinic proton at δ 6 82 ppm, whereas both epoxide protons are found as narrow triplets at δ 4 01 and 4 19 ppm, respectively

In contrast to **8b** and **9b**, parent tricyclic epoxy-alcohol **8a** and its acetate **9a** did not show an effective cycloreversion below 500 °C. Neither epoxycyclopentenol **12a** nor its acetate **13a** were detected among the pyrolysis products at this temperature. At an optimum temperature of 600 °C (2.10^{-2} torr), the cycloreversion of both alcohol **8a** and its acetate **9a** was complete, to give a mixture of (E)- and (Z)-pentadienoic acids **14a**[16] as the main products in a yield of *ca.* 50 % (Scheme 6). Besides these acids **14a**, small amounts of but-3-enal **15a**[17] (20 %) and crotonaldehyde **15b** (10 %) were formed in the case of thermolysis of **8a**. The pentenoic acids **14a** could readily be isolated from the pyrolysate by an acid-base extraction.

Similar results were recently reported by Adam and Pasquato[18] who also studied the thermal cycloreversion of epoxytricyclodecenol **8a**. Using a long quartz tube of 60 cm, these authors found that the temperature required to accomplish a complete cycloreversion amounted to 520 °C. However, even at this relatively low temperature, only a mixture of (E)- and (Z)-2,4-pentadienoic acids **14a** was obtained. The formation of butenals was not reported.

Scheme 6

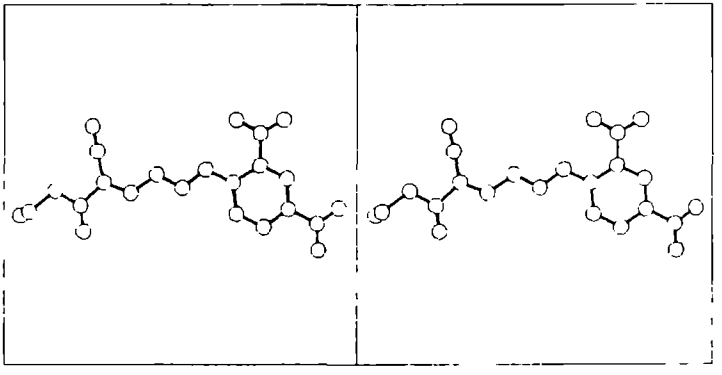


When epoxy-alcohol **8b** was subjected to FVT at temperatures of 490 °C or higher, the amount of epoxycyclopentenol **12b** originally formed, rapidly decreased with increasing temperature in favor of open chain compounds (Scheme 5). At 490 °C, a mixture of three products was isolated from the

pyrolysate among which only a trace of starting material **8b**. The major products appeared to be epoxycyclopentenol **12b** and butenal derivative **16**, which was isolated from the mixture together with its structural isomer **17**[19] in a total yield of 21 %. Besides these aldehydes, the presence of *cis*- and *trans*-2-ethoxycarbonyl-2,4-pentadienoic acid **14b** was deduced from the ^{1}H-NMR spectrum of the crude pyrolysate (Scheme 5). When the FVT of **8b** was carried out at 570 °C a crude mixture of **16**, **17** and **14b** was obtained. In this case the acids **14b** were isolated by an acid-base extraction in a yield of 24 %.

The acetate **9b** behaved different in comparison with the corresponding alcohol **8b** when subjected to flash vacuum thermolysis at a temperature exceeding 525 °C. This temperature was too high for the initially formed epoxycyclopentenol acetate **13b** to survive. The presence of an acetoxy group instead of a hydroxyl group strongly effects the subsequent thermal rearrangement as only a small amount (5 %) of the pentadienoic acid **14b** was obtained. The major product in this thermolysis was the highly unsaturated aldehyde **18b**. Unambiguous assignment of the stereochemistry around its olefinic bond was obtained after an X-ray diffraction study[20] of the 2,4-dinitrohydrazone derivative **19b** (Fig. 3). This clean thermal formation of a pentenynal does not seem to be a general feature of tricyclic epoxy acetates **9**, because thermolysis of the parent epoxytricyclodecenol acetate **9a** under similar conditions afforded a complex mixture, among which no such compound could be detected. It cannot be ruled out completely that pentenynal **18a**[21] is not formed in this reaction, because it will be thermally too unstable to be isolated *(vide infra)*.

Fig. 3



The flash vacuum thermolysis of bisacetate **9c** was also investigated as it will shed some light on the importance of the presence of a substituent at the angular position of the tricyclic precursor **9**. At an optimum temperature of 500 °C this thermolysis slowly afforded pentenynal **18c** in 70 % yield, which again was readily converted to its crystalline 2,4-dinitrohydrazone derivative **19c** (Scheme 6). This result proves that conjugative stabilization of the pentenynal, *e.g.* by an ester function like in **18b**, is not necessary for its formation or its isolation. However, in view of the negative results with parent

acetate **9a** it seems that some angular substitution in the tricyclic system stabilizes the pentenynal formed on thermolysis

An analysis of the results described above clearly reveals the stabilizing effect of the angular ester function in epoxytricyclodecenols **8** and their acetates **9** on the thermal stability of the epoxypentenols **12** and **13**, initially produced during the thermolysis This is expressed in the isolation of these compounds from alcohol **8b** and its acetate **9b**, and the relatively low thermolysis temperatures needed to achieve an efficient cycloreversion reaction In all other cases, further thermal rearrangements and fragmentations of the species **12** and **13** take place to form either carboxylic acids **14** (in the case of **8a** and **9a**) or pentenynals **18** (in the case of **9c**)

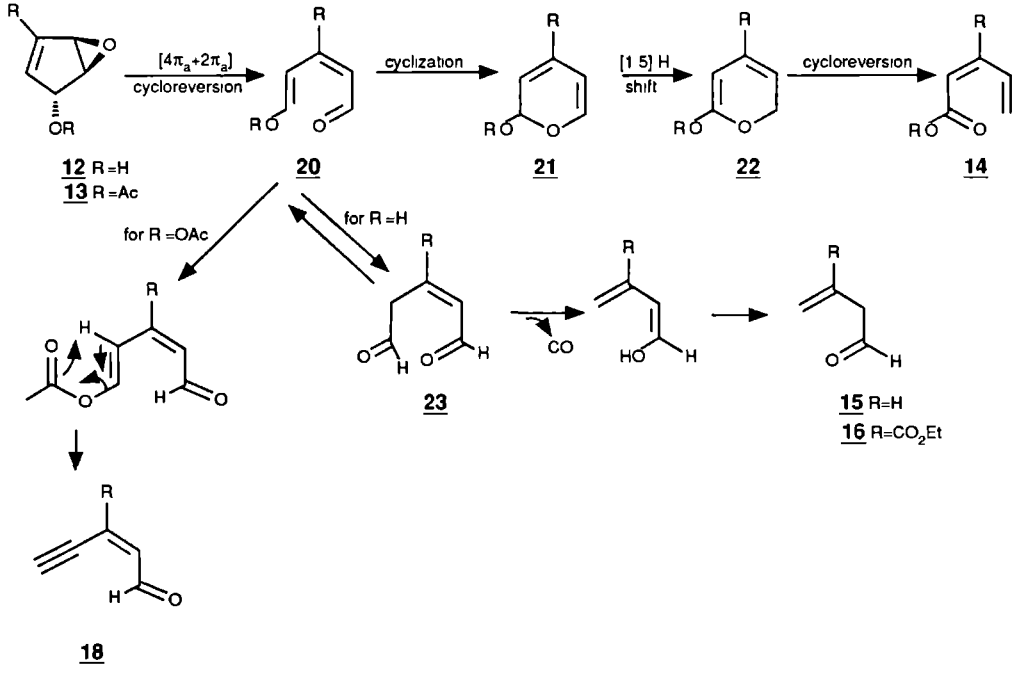
In analogy with the thermal rearrangement[15] of cyclopentadienone oxides **10**, the initial step in the thermal degradation of 4,5 epoxycyclopentenols **12** and their acetates **13** presumably involves a $[4\pi_a+2\pi_a]$ cycloreversion to afford the unsaturated aldehyde **20**[22] (Scheme 7) Based on the ultimate formation of α-pyrones from cyclopentadienone oxides (Scheme 4) and their acetals, the most plausible next step will be a pyrane ring closure of **20** involving a synchronous 6π-electrocyclic ring closure to form **21** A [1,5] H-shift then leads to **22**, which upon electrocyclic reversion produces the 2,4-pentadienoic acid **14** as the final product Adam and Pasquato[18] present a similar mechanism, but they suggest that the formation of **22** from **20** involves the initial addition of the enol alcohol function to the aldehyde group in a non synchronous nucleophilic addition step However, our observation that both alcohol **8a** and its acetate **9a** behave alike and produce the same pentadienoic acid **14** in about the same yield, makes their explanation unlikely, because nucleophilic addition of the enol acetate moiety to the aldehyde function is not possible Furthermore, the earlier observation[15] that the dimethyl acetals of cyclopentadienone oxides, which are structurally related to **12** and **13**, readily afford high yields of the dimethyl acetals of the corresponding α pyrones, also strongly pleads against such a non-synchronous pyrane formation

The formation of the aldehydes **15** and **16** observed for the substrates **8a** and **8b** during the flash vacuum thermolysis above 500 °C, can be rationalized by assuming that **20** undergoes initial tautomerization to form *cis* pentenedial **23** This dialdehyde may undergo decarbonylation, as depicted in the mechanistic Scheme 7, to form the observed aldehydes **15** and **16** There is ample precedent[23] for such thermal decarbonylation reactions of aliphatic aldehydes at temperatures around 500 °C in the gas phase

Finally, the intermediacy of **20** also forms the clue for the ultimate formation of pentenynals **18** on flash vacuum thermolysis of acetates **9b** and **9c** Due to the concerted character of the formation of **20** from epoxytricyclodecenol acetates **9**, it is logical that the enol acetate has the E-configuration Herein the acetate function has the correct position to undergo a thermally induced *syn* elimination[24] to form the observed pent-2 en 4 ynals **18** (Scheme 7)

Despite the relatively simple structure of the pentenynals **18**, only a few synthetic routes to these structures are known Hoffman *et al*[21] obtained the very reactive parent pentenynal **18a** and some of

Scheme 7



its congeners by thermal decomposition of the sodium salt of furfural tosylhydrazone Although **18a** is stable at -78 °C, this unusually conjugated aldehyde resinifies rapidly at ambient temperature Our route to these compounds, starting from epoxytricyclodecenol acetates **9**, may offer a synthetic alternative for more stable derivatives of **18**, *e g* **18b** and **18c**

The results presented here show that flash vacuum thermolysis of epoxytricyclodecenols **8** (and their acetates **9**) only affords the corresponding 2,3-epoxycyclopentenols (or acetates), if the temperature, required for an efficient cycloreversion, is sufficiently low to prevent further thermal rearrangement Sofar, this approach is limited to those tricyclic precursors which possess a π-containing function at the angular C_2-position The thermal behavior of epoxytricyclodecenols (and their acetates) show a considerable resemblance with those of the corresponding epoxytricyclodecenones and their acetals

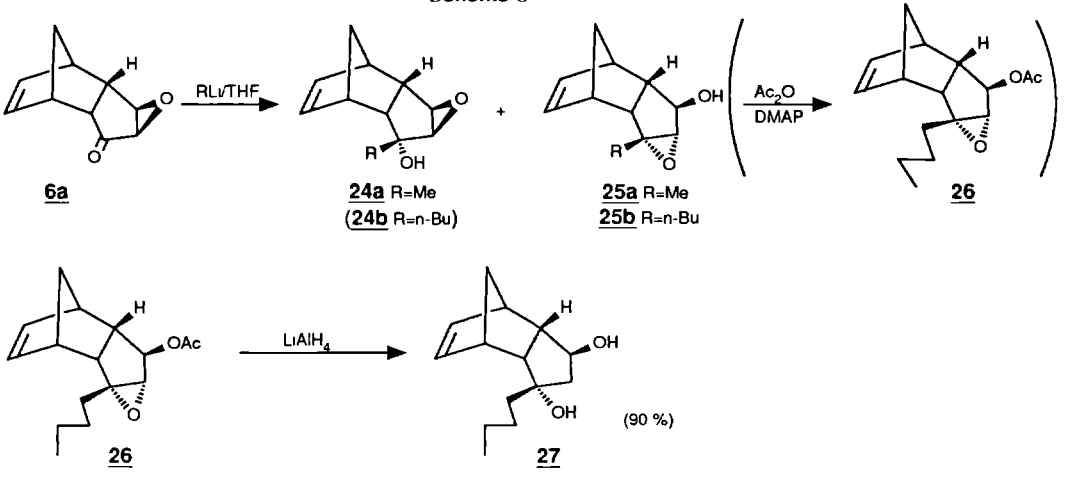
6 4 INTRAMOLECULAR EPOXIDE RING OPENING REACTIONS OF EPOXYTRICYCLODECENOLS

An interesting characteristic of tricyclic epoxyketones **6** is their reluctance to undergo intermolecular epoxide ring opening[25] Although epoxides normally smoothly react with $LiAlH_4$, the epoxide ring in **6** remains unaffected The explanation for this behavior of **6** is the steric shielding of its *con-*

cave side for nucleophilic attack. Although useful in some cases, this low reactivity of the epoxide function in **6** limits its synthetic applicability. It is of interest to compare the reactivity of the epoxide function in the corresponding epoxytricyclodecenols **8**; in particular the possibility of an intramolecular reaction with the alcohol function is worth considering. An example of such an intramolecular reaction was encountered by Bergmann and Magnusson[26] in the reaction of 4,4-dimethyl-*trans*-2,3-epoxycyclohexanol with bases.

As reported above, epoxytricyclodecenone **6a** is readily reduced with LDA or $NaBH_4$ to form exclusively the *endo*-alcohol-*exo*-epoxide **8a** in high yields. Another method to obtain suitable epoxytricyclodecenols for this study is the reaction of the ketones **6a** with organometallic reagents. Reaction of **6a** with MeLi afforded a mixture of two epoxides in a ratio of 5:1, to which on basis of their spectral and chemical properties *(vide infra)*, structures **24a** and **25a** were assigned (Scheme 8). The formation of product **25a** can readily be explained by invoking an intramolecular epoxide opening. Apparently, the replacement of a hydrogen atom at C_3 in **8a** by a methyl group promotes such an intramolecular epoxide ring opening. This effect is even more pronounced for a *n*-butyl group. Reaction of **6a** with *n*-BuLi gave only one product in a yield of 77 %, which appeared to be epoxide **25b**. Subsequent acylation of **25b** with acetic anhydride and DMAP gave the corresponding acetate **26** (Scheme 8).

Scheme 8



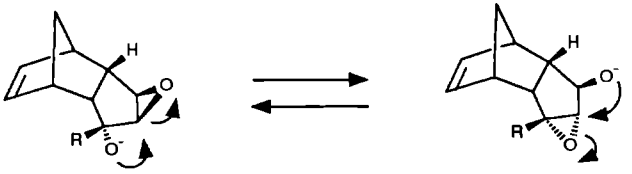
6a **24a** R=Me (**24b** R=n-Bu) **25a** R=Me **25b** R=n-Bu **26** **26** **27**

Comparison of the ^{1}H-NMR spectra of the stereoisomers **24a** and **25a**, revealed some characteristic differences which allowed an unequivocal assignment of their structures (see experimental part). An independent chemical proof for the formation of the inverted epoxides **25a** and **25b** was obtained from the reduction product of acetate **26** with $LiAlH_4$ at ambient temperature. As the epoxide function in **26** now is favorably oriented toward nucleophilic attack, facile reductive opening of the epoxide ring may be expected. Indeed, in a regio- and stereoselective conversion, diol **27** was rapidly produced in a yield of 90 %.

The extent of the intramolecular epoxide opening, which increases in the order **8a**<**24a**<**24b**, may

be explained by both steric and electronic effects. Assuming the initial formation of alcoholate **28** by stereospecific addition to the C_3 ketone function in **6a**, subsequent intramolecular epoxide ring opening leads to alcoholate **29**. Under the conditions used, the ultimate product formation will depend only on the thermodynamic stabilities of the respective lithium alcoholates **28** and **29**, assuming that the reaction time is sufficiently long to allow complete equilibration (Scheme 9).

Scheme 9



28 **29**

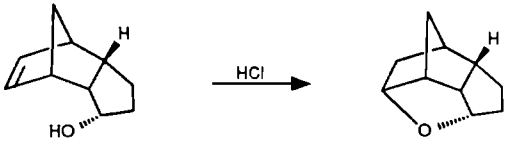
The alkyl group R may exert a buttressing effect in **28**, thus shifting the equilibrium toward **29**. The fact that for the large *n*-butyl substituent only **29** was isolated is in accordance with this suggestion. For the epoxytricyclodecenol **8a** no such intramolecular epoxide opening was observed, this reaction is apparently thermodynamically unfavorable.

These preliminary results show that stereochemical inversion of the epoxide function in tricyclic epoxy alcohols **24** is feasible. Further studies are needed to establish the scope of this intramolecular substitution reaction and to determine the synthetic prospects of the new epoxy-alcohols **25**.

6.5 ACID-CATALYZED FORMATION OF AN OXA-CAGE ALCOHOL FROM TRICYCLIC EPOXY-ALCOHOL **8b**

Recently, a facile acid-catalyzed ring closure of *endo*-carbinol **30** to oxatetracycloundecane **31** was reported by Bird *et al*[27] (Scheme 10). The epoxytricyclodecenols **8** also have their hydroxy function appropriately positioned for a similar ring closure reaction. Therefore, compound **8b** was subjected to conditions that would induce an intramolecular addition of the hydroxy function to the proximate double bond.

Scheme 10

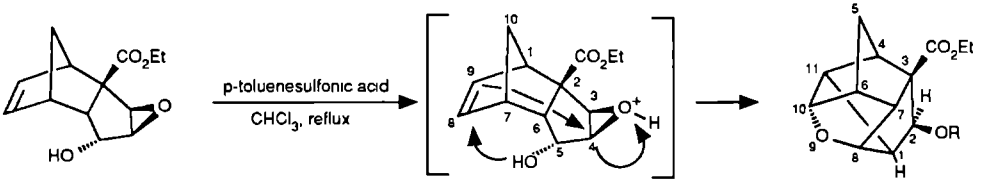


30 **31**

In a preliminary experiment, **8b** was heated in chloroform under reflux in the presence of *p*-toluenesulfonic acid (PTS) for two hours. A mixture of products was obtained in a ratio of 2:1, according to a Capillary GC analysis. Although the main product could not be obtained pure by flash chromato-

graphy, the ^{1}H-NMR spectrum of the product mixture revealed that olefinic and epoxide protons were no longer present. The IR spectrum indicated the presence of an alcohol function. Finally, GC/MS analysis showed the molecular mass of the major product to be the same as that of the starting alcohol **8b**. These spectroscopic results strongly suggest the occurrence of the anticipated intramolecular addition to the olefinic bond in **8b**, followed by an intramolecular epoxide ring opening to afford oxa-cage compound **33** (Scheme 11). Both molecular models and MM2-calculations show the feasibility of such a *trans*-annular epoxide ring opening by a developing nucleophilic center at C_9 in **32**.

Scheme 11



8b **32** **33** R=H **34** R=Ac

In order to further elucidate the structure of this unknown compound, it was acylated with acetic anhydride to give the crystalline acetate **34**. In addition to a correct elemental microanalysis and the expected molecular ion (*m/e* 278), the most informative structural information is provided by its ^{1}H-NMR spectrum (400 MHz). As expected, this indicates the presence of one methylene group (at C_5), which appears as a characteristic AB-pattern at δ 1.51 and 1.55 ppm, respectively. Furthermore, the presence of eight separate signals, with an integration value of one hydrogen atom each, is in nice accordance with the presence of H_1, H_2, H_4, H_6, H_7, H_8, H_{10} and H_{11}, respectively. The lowest field proton (δ 5.35 ppm) of **34** appears as a doublet (J=2.3 Hz). This coupling constant agrees well with the $^3J_{H1,H2}$ value of 2.2 Hz, which was calculated after MM_2-structure optimization of **34**. As no crystals suitable for an X-ray diffraction study could be grown yet, no definite proof for structure **33** could be obtained. Further attempts will be made to secure the structure of **33** and to explore this interesting acid-catalyzed reaction for other substituted epoxytricyclodecenols **8**.

6 6 EXPERIMENTAL PART

General

The remarks given in Section 2 5 also apply here

Syntheses

Exo 4,5 *epoxy*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*en*-endo-3-*ol* **8a**

To a stirred soln of diisopropylamine (0 101 g, 1 00 mmol) in dry THF (5 ml) under N_2, was gradually added a 1 6 M soln of *n*-BuLi in *n* hexane (1 0 ml, 1 6 mmol) at 0 °C using a syringe After 20 min, the mixture was cooled to -78 °C and a soln of **6a** (0 14 g, 0 86 mmol) in THF was added using a syringe After 15 min the mixture was treated with MeI (0 30 g, 2 11 mmol) in THF (10 ml) The yellow soln was then allowed to attain r t and stirred for 30 min The resulting brown soln was quenched with an excess NH_4Cl aq at 0 °C, extracted with Et_2O (3x25 ml), washed with water (3x20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give crude **8a** Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3) afforded **8a** (85 mg, 60 %) as an oil which solidified slowly

In an alternative procedure, $NaBH_4$ (60 mg, 1 59 mmol) was suspended in dry THF (10 ml) and cooled to 0 °C To this suspension was added **6a** (0 160 g, 0 99 mmol) in dry THF (5 ml) After stirring for 90 min the reaction was worked up as described above, to yield **8a** (0 154 g, 95 %) after flash chromatography as a white solid, m p 62-65 °C (after recrystallization from EtOH) ^{1}H-NMR δ 1 36 A of AB (d, J=7 7 Hz, 1H, H_{10}), 1 51 B of AB (d, J=7 7 Hz, 1H, H_{10}), 1 99 (br d, J=5 4 Hz, 1H, OH), 2 92 (m, 4H, H_2, H_4, H_5, H_6), 3 23 (s, 2H, H_1, H_7), 4 22 (m, 1H, H_3), 5 93-6 33 (m, 2H, H_8, H_9), ^{13}C-NMR δ 43 7 (d), 45 0 (d), 49 8 (d), 51 6 (t, C_{10}), 53 3 (d, C_1, C_2, C_6, C_7), 61 5 (d), 63 9 (d, C_4, C_5), 72 1 (d, C_3), 131 9 (d), 136 7 (d, C_8, C_9), IR (CCl_4) ν 3700-3100 (OH), 1635 (C=C) cm^{-1}, CI/MS m/e 165 (M^++1), 147 (M+1 H_2O), 129, 99 (M+1 C_5H_6), 66, Found 165 0910 $C_{10}H_{13}O_2$ requires 165 0916

Ethyl exo 3,4 *epoxy* endo 5-*hydroxy* endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* 2 *carboxylate* **8b**

The same procedure as described for the LDA reduction of **6a**, using **6b** (0 92 g, 3 93 mmol) afforded **8b** (0 74 g, 80 %) The reduction of **6b** (0 65 g, 2 78 mmol) yielded **8b** (0 62 g, 95 %) after flash chromatography as a pure oil ^{1}H-NMR δ 1 34 (t, J=7 0 Hz, 3H, CH_3), 1 47 A of AB (d, J=8 0 Hz, 1H, H_{10}), 1 69 B of AB (d, J=8 0 Hz, 1H, H_{10}). 2 13 (br s, 1H, OH), 3 05 (br s, 1H, H_7), 3 16 (br s, 1H, H_1), 3 27 (d, J=2 1 Hz, 1H, H_4), 3 43 (m, 1H, H_6), 3 47 (d, J=2 1 Hz, 1H, H_3), 4 23 (q, J=7 0 Hz, 2H, OCH_2), 4 30 (d, J=8 0 Hz, 1H, H_5), 6 14 (dd, J=5 6 Hz, J=2 8 Hz, 1H, H_8 or H_9), 6 38 (dd, J=5 6 Hz, J=2 8 Hz, 1H, H_8 or H_9), IR (CCl_4) ν 3620 (OH), 1735 (C=O), 1540, 1235 cm^{-1}, CI/MS m/e 237 (M^++1), 219 (M+1-H_2O), 191, 153 (M+1 H_2O C_5H_6), 145, Found 237 1125 $C_{13}H_{17}O_4$ requires 237 1127

Exo-4,5-*epoxy*-6-*hydroxymethyl*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*en*-endo-3-*ol* **8c**

Ketone **6b** (0.79 g, 3.38 mmol) was dissolved in dry Et_2O and added to a stirred suspension of $LiAlH_4$ (0.70 g, 18 mmol) in Et_2O. After 30 min the resulting mixture was hydrolyzed with water, acidified to pH 7 and subjected to continuous extraction (Et_2O) for 2 days. The organic layer was separated, washed, dried ($MgSO_4$) and evaporated *in vacuo* to produce crude **8c** (0.61 g, 93 %). Flash chromatography gave **8c** (0.49 g, 75 %) as an oil which solidified slowly. Recrystallization from EtOH /*n*-hexane afforded a pure sample. M.p. 104 °C. ^{1}H-NMR: δ 1.58 (br s, 2H, H_{10}), 1.73-2.21 (m, 1H, OH), 2.50-3.10 (m, 1H, OH), 2.62 (dd, J=7.6 Hz, J=3.9 Hz, 1H, H_2), 2.71 (br s, 1H, H_1 or H_7), 2.93 (br s, 1H, H_1 or H_7), 3.15 (d, J=2.3 Hz, 1H, H_4 or H_5), 3.24 (d, J=2.3 Hz, 1H, H_4 or H_5), 3.69 A of AB (d, J=11.1 Hz, 1H, C_6-CH_2), 3.89 B of AB (d, J=11.1 Hz, 1H, C_6-CH_2), 4.24 (d, J=7.6 Hz, 1H, H_3), 6.04-6.19 (m, 1H, H_8 or H_9), 6.19-6.37 (m, 1H, H_8 or H_9); IR (NaCl): 3700-3000 (OH), 1640 (C=C) cm^{-1}; CI/MS: m/e 195 (M^++1), 177 (M+1-H_2O), 159 (M+1-2H_2O), 111 (M+1-H_2O-C_5H_6), 66; Found 195.1023. $C_{11}H_{15}O_3$ requires 195.1021.

Endo-3-*acetoxy*-exo-4,5-*epoxy*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*ene* **9a**

Alcohol **8a** (0.40 g, 2.44 mmol) was added to a mixture of Ac_2O (0.68 g, 6.67 mmol) in pyridine (0.65 g, 8.23 mmol) and stirred for 48 h at r.t. An excess of $NaHCO_3$ aq was added and the soln was stirred for 30 min. After extraction using Et_2O (3x), drying ($MgSO_4$) and concentration, crude **9a** was obtained as an oil. Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3) gave pure **9a** (0.39 g, 78 %) as a white solid, m.p. 31.5-32.5 °C (after recrystallization from EtOH). ^{1}H-NMR: δ 1.33 A of AB (d, J=6.6 Hz, 1H, H_{10}), 1.49 B of AB (d, J=6.6 Hz, 1H, H_{10}), 2.12 (s, 3H, $COCH_3$), 2.71-2.88 (m, 1H, H_1 or H_7), 2.88-3.01 (m, 1H, H_1 or H_7), 2.95 (d, J=3.2 Hz, 1H, H_6), 3.00 (dd, J=7.8 Hz, J=3.9 Hz, 1H, H_2), 3.20 (d, J=2.1 Hz, 1H, H_4 or H_5), 3.30 (d, J=2.1 Hz, 1H, H_4 or H_5), 4.97 (d, J=7.6 Hz, 1H, H_3), 6.07 (m, 2H, H_8, H_9); IR (KBr): ν 1740 (C=O) cm^{-1}; CI/MS: m/e 207 (M^++1); EI/MS: m/e 206 (M^+), 163, 146 (M-CH_3COOH), 140 (M-C_5H_6), 66; Found 207.1025. $C_{12}H_{15}O_3$ requires 207.1021.

Ethyl endo-5-*acetoxy*-exo-3,4-*epoxy*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*ene* 2-*carboxylate* **9b**

The same procedure as described for the preparation of **9a** was used, starting from **8b** (0.98 g, 4.15 mmol), with the exception of the reaction time which was 24 h. **9b** (1.10 g, 95 %) was obtained as a pure solid after flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3). M.p. 48-49 °C (after recrystallization from EtOH). ^{1}H-NMR: δ 1.30 (t, J=7.1 Hz, 3H, $OCH_2\mathbf{CH_3}$), 1.45 A of AB (d, J=8.7 Hz, 1H, H_{10}), 1.70 B of AB (d, J=8.7 Hz, 1H, H_{10}), 2.11 (s, 3H, $COCH_3$), 2.86 (br s, 1H, H_1 or H_7), 3.14 (br s, 1H, H_1 or H_7), 3.33 (d, J=2.0 Hz, 1H, H_3 or H_4), 3.46 (d, J=2.0 Hz, 1H, H_3 or H_4), 3.52 (dd, $J_{5,6}$=7.9 Hz, $J_{6,7}$=4.0 Hz, 1H, H_6), 4.21 (q, J=7.1 Hz, 2H, OCH_2), 5.02 (d, J=7.9 Hz, 1H, H_5), 6.12-6.34 (m, 2H, H_8, H_9); ^{13}C-NMR δ 13.9 (q, CH_2CH_3), 20.4 (q, $COCH_3$), 45.5 (d), 49.0 (t, C_{10}), 49.7 (d), 54.3 (d, C_1, C_6, C_7), 60.9 (t, OCH_2), 62.1 (d), 62.2 (d, C_3, C_4), 65.3 (s, C_2), 73.0 (d, C_5), 131.7 (d), 138.9 (d, C_7, C_8), 169.8 (s, C_2-$OCOCH_3$), 173.5 (s, C_2-CO); IR (KBr): ν 1725 (C=O), 1230 cm^{-1}; CI/MS: m/e 279 (M^++1), 237, 219 (M-CH_3COOH), 191, 173, 153, 145, 125; Found C, 64.80; H, 6.77.

$C_{15}H_{18}O_5$ requires C, 64.74; H, 6.52.

Endo-3-*acetoxy*-6-*acetoxymethyl*-exo-4,5-*epoxy*-endo-*tricyclo*[5.2.1.$0^{2,6}$]*dec*-8-*ene* **9c**

The same procedure as described for the preparation of **9a** was used, starting from **8c** (0.6 g, 3.09 mmol) and Ac_2O (4 ml) in pyridine (7 ml) to yield crude **9c** (pur. 84 %, Cap. GC), after reacting for 72 h. Purification by bulb to bulb distillation gave pure **9c** (0.69 g, 80 %) as an oil. ^{1}H-NMR: δ 1.38 A of AB (d, J=7.5 Hz, 1H, H_{10}), 1.75 B of AB (d, J=7.5 Hz, 1H, H_{10}), 2.10 (s, 6H, 2x$COCH_3$), 2.54 (dd, J=7.4 Hz, J=3.9 Hz, 1H, H_2), 2.73 (br s, 1H, H_1 or H_7), 2.92 (br s, 1H, H_1 or H_7), 3.25 (d, J=1.8 Hz, 1H, H_4 or H_5), 3.36 (d, J=1.8 Hz, 1H, H_4 or H_5), 4.06 A of AB (d, J=10.8 Hz, 1H, C_6-CH_2), 4.31 B of AB (d, J=10.8 Hz, 1H, C_6-CH_2), 4.94 (d, J=7.4 Hz, 1H, H_3), 6.16 (br s, 2H, H_8, H_9); IR (CCl_4): ν 1740 (C=O), 1220 cm^{-1}; CI/MS: m/e 279 (M^++1), 237, 219 (M+1-HOAc), 177, 159, 153, 111, 66(C_5H_6), 60 (HOAc); Found 279.1229. $C_{15}H_{19}O_5$ requires 279.1232.

FVT of **8a**

Alcohol **8a** (80 mg, 0.49 mmol) was subjected to FVT [sample temp.: 120 °C, oven temp.: 600 °C, p: 2.10^{-2} mm Hg, oven lenght: 16 cm, cold trap temp.: -196 °C]. After completion of the FVT, the cold trap surface was rinsed with $CDCl_3$. Subsequent ^{1}H-NMR analysis revealed the formation of a mixture consisting of **14a**, **15a**, **15b** and cyclopentadiene. The aldehydes **15a** and **15b** were formed in a molar ratio of 13:5, in *ca.* 25 % and 10 % yield, respectively. These aldehydes were not isolated, but some of their characteristic signals were present in the ^{1}H-NMR spectrum of the crude reaction mixture. The spectral data of **15a** closely corresponded to those reported by Havel and Chan[17]. The signals of **15b** were identical to those of a purchased sample. *But*-3-*enal* **15a**: ^{1}H-NMR: δ 3.20 (br d, J=6.8 Hz, 2H, H_2), 5.15 (br d, J=10 Hz, 1H, H_4), 9.71 (t, J=1.9 Hz, 1H, H_1). *But*-2-*enal* **15b**: ^{1}H-NMR: δ 2.15 (dd, J=7.4 Hz, J= 1.8 Hz, 3H, H_4), 9.58 (d, J=7.6 Hz, 1H, H_1). The acids **14a**[16] (23 mg, 48 %) were isolated as a *cis/trans*-mixture after acid-base extraction (*Cf.* FVT of **9a**).

FVT of **8b**.

Experiment 1: **8b** (74 mg, 0.314 mmol) was subjected to FVT [sample temp.: 80 °C, oven temp.: 430 °C, p: 10^{-2} mm Hg, oven lenght: 16 cm, cold trap temp.: -196 °C] to produce a 13:7 molar mixture of **12b** and **8b**. This mixture was separated by careful bulb to bulb distillation to yield *ethyl* 4,5-*epoxy*-trans-3-*hydroxycyclopent*-1-*ene carboxylate* **12b** (25 mg, 47 %) as a yellow oil which was contaminated with a trace of **8b**. **12b**: ^{1}H-NMR: δ 1.31 (t, J=7 Hz, 3H, OCH_2CH_3), 3.98 (t, J=2 Hz, 1H, H_4 or H_5), 4.07-4.38 (m, 5H, OCH_2, OH, H_3, H_4 or H_5,), 6.88 (q, J=2 Hz, 1H, H_2).

Experiment 2: **8b** (85 mg, 0.360 mmol) was subjected to FVT [sample temp.: 95 °C, oven temp.: 490 °C, p: 2.10^{-2} mm Hg, cold trap temp.: -78 °C] to produce 55 mg of a crude mixture of **12b**/**14b**/**16**/**17** and a trace of **8b**. Flash chromatography (silica gel, $CHCl_3$) gave pure **16** (8 mg, 16 %) and a mixture which mainly consisted of **16** and **17** (15 mg). The acids **14b** (*vide infra*) were not isolated. *Ethyl* 2-*methylidene*-4-*oxobutanoate* **16**: ^{1}H-NMR: δ 1.31 (t, J=7 Hz, 3H, CH_3), 3.42 (br s, 2H,

H_3), 4.24 (q, J=7 Hz, 2H, OCH_2), 5.73 (br d, J=0.9 Hz, 1H, C_2-CH), 6.42 (br s, 1H, C_2-CH), 9.71 (d, J=1.5 Hz, 1H, H_4); IR (CCl_4): ν 1720 (C=O), 1685 (C=O) cm^{-1}; CapGC/EI/MS: m/e 142 (M^+), 96 (M-C_2H_5OH), 68 (M-CO-HOEt); Found 142.0628. $C_7H_{10}O_3$ requires 142.0630. *Ethyl 2-methyl-4-oxo-(E)-but-2-enoate* **17**[19]: ^{1}H-NMR: δ 1.33 (t, J=7 Hz, 3H, CH_3), 2.32 (d, J=1.5 Hz, 3H, C_2-CH_3), 4.29 (q, J=7 Hz, 2H, OCH_2), 6.80 (m, 1H, H_3), 10.21 (d, J=7.6 Hz, 1H, H_4); IR (CCl_4): ν 1720 (C=O), 1685 (C=O) cm^{-1}; EI/MS: m/e 142 (M^+), 96 (M-C_2H_5OH), 68 (M-CO-HOEt).

Experiment 3: **8b** (100 mg, 0.424 mmol) was subjected to FVT [sample temp.: 80 °C, oven temp.: 570 °C, p: 6.10^{-2} mm Hg with additional N_2-inlet, oven lenght: 16 cm, cold trap temp.: -196 °C] to yield a crude mixture of **14b**, **16** and **17**. A mixture of **16** and **17** (15 mg, 25 %) was obtained after flash chromatography. A 2:1 molar mixture of cis/trans-*2-carboethoxybuta-1,3-diene carboxylic acid* **14b** (17 mg, 24 %) was isolated as an oil after acid-base extraction (Et_2O). ^{1}H-NMR: *trans*-**14b**: δ 1.35 (t, J=7.1 Hz, 3H, CH_3), 4.35 (q, J=7.1 Hz, 2H, OCH_2), 5.47-5.78 (m, 2H, H_4), 5.91 (br s, 1H, H_1), 6.47 (dd, J=17.6 Hz, J=10.0 Hz, 1H, H_3), 7.16-7.71 (br s, 1H, OH); *cis*-**14b**: δ 1.35 (t, J=7.1 Hz, 3H, CH_3), 4.31 (q, J=7.1 Hz, 2H, OCH_2), 5.67 (br d, $^3J_{cis}$=11.2 Hz, 1H, H_4), 5.98 (br d, $^3J_{trans}$=17.6 Hz, 1H, H_4), 6.35 (br s, 1H, H_1), 7.16-7.71 (br s, 1H, OH), 7.49 (ddd, J=17.6 Hz, J=11.2 Hz, J=0.7 Hz, 1H, H_3); IR (CCl_4): ν 3600-2450 (OH), 1730 (C=O), 1695 (C=O) cm^{-1}; EI/MS: m/e 170 (M^+), 124 (M-C_2H_5OH), 96; Found 170.0574. $C_8H_{10}O_4$ requires 170.0579.

Ethyl trans-3-*acetoxy*-4,5-*epoxycyclopent*-1-*ene carboxylate* **13b**

Acetate **9b** (52 mg, 0.19 mmol) was subjected to FVT [sample temp.: 70 °C, oven temp.: 460 °C, p: 2.10^{-2} mm Hg, cold trap temp.: -196 °C] to produce **13b** (20 mg, 50 %) as a NMR-pure oil after bulb to bulb distillation. ^{1}H-NMR: δ 1.34 (t, J=6.9 Hz, 3H, $OCH_2\mathbf{CH_3}$), 2.13 (s, 3H, $COCH_3$), 4.01 (t, J=2.1 Hz, 1H, H_4 or H_5), 4.19 (t, J=2.1 Hz, 1H, H_4 or H_5), 4.31 (q, J=6.9 Hz, 2H, OCH_2), 5.60 (t, J=2.1 Hz, 1H, H_3), 6.82 (dd, J=4.2 Hz, J=2.1 Hz, 1H, H_2); IR (CCl_4): ν 1740 (C=O), 1620 (C=C) cm^{-1}; CI/MS: m/e 213 (M^++1), 171, 153 (M+1-CH_3COOH), 125; Found 213.0764 (M+1). $C_{10}H_{13}O_5$ requires 213.0763.

Cis/trans-*buta*-1,3-*diene carboxylic acid* **14a**

Acetate **9a** (72 mg, 0.35 mmol) was subjected to FVT [sample temp.: 45 °C, oven temp.: 620 °C, p: 2.10^{-2} mm Hg, oven lenght: 30 cm, cold trap temp.: -196 °C] to yield **14a** (22 mg, 64 %) as a NMR-pure oil, after acid-base extraction using Et_2O. ^{1}H-NMR: The spectral data were identical to those reported by Kirmse *et al*[16]; IR (CCl_4): ν 3500-2300 (OH), 1690 (C=O), 1635 (C=C) cm^{-1}; CI/MS: m/e 99 (M^++1), 83, 81 (M+1-H_2O), 55 (M+1-CO_2).

Ethyl 1-*oxo-(E)-pent*-2-*en*-4-*yne* 3-*carboxylate* **18b**

Acetate **9b** (58 mg, 0.21 mmol) was subjected to FVT [sample temp.: 80 °C, oven temp.: 525 °C, p: 6.10^{-2} mm Hg with additional N_2-inlet, oven lenght: 16 cm, cold trap temp.: -196 °C] to yield **18b** (16 mg, 50 %) as a pure oil after flash chromatography (silica gel, EtOAc /*n*-hexane = 1/3). ^{1}H-NMR: δ

1 37 (t, J=6 9 Hz, 3H, OCH_2CH_3), 3 71 (d, J=0 9 Hz, 1H, H_5), 4 34 (q, J=6 9 Hz, 2H, OCH_2), 7 15 (dd, J=7 8 Hz, J=0 9 Hz, 1H, H_2), 10 25 (d, J=7 8 Hz, 1H, H_1), IR (CCl_4) ν 3300 (alkyne), 2105 (alkyne), 1740 (C=O), 1685 (C=O) cm^{-1}, CI/MS m/e 153 (M^++1), 125 (M+1 CO), 107, Found 153 0555 (M+1) $C_8H_9O_3$ requires 153 0552

3-*Acetoxymethyl*-(E)-*pent* 2 *en* 4 *ynal* **18c**

Diacetate **9c** (67 mg, 0 24 mmol) was subjected to FVT [sample temp 70 °C, oven temp 500 °C, p $6\ 10^{-2}$ mm Hg with additional N_2-inlet, oven lenght 30 cm, cold trap temp -196 °C] to afford **18c** (5 mg, 66 % from 0 05 mmol converted **9c**) as a pure oil after flash chromatography (silica gel, EtOAc /*n* hexane = 1/2) After the FVT, unchanged **9c** (53 mg, 0 19 mmol) was recovered from the sample flask ^{1}H-NMR δ 2 15 (s, 3H, $COCH_3$), 3 57 (s, 1H, H_5), 4 75 (d, J=1 6 Hz, 2H, C_3-CH_2), 6 37 (br d, J=7 6 Hz, 1H, H_2), 10 11 (d, J=7 6 Hz, 1H, H_1), IR (CCl_4) ν 3200 (alkyne), 1760 (C=O), 1690 (C=O), 1605 (C=C) cm^{-1}, EI/MS m/e 110 (M^+ C_2H_2O), 92 (M-CH_3COOH), 82, 63, 43, Found 110 0352 (M-C_2H_2O) $C_6H_6O_2$ requires 110 0367

Ethyl 1-*(2,4-dinitrophenyl)hydrazino* (E)-*pent*-2-*en*-4-*yne* 3-*carboxylate* **19b**

To a soln of 2,4 dinitrophenylhydrazine (0 25 g, 1 26 mmol) and H_2SO_4 (0 5 ml) in MeOH (3 ml) was added **18b** (0 15 g, 0 987 mmol) to furnish[28] **19b** (272 mg, 83 %) as red crystals M p 150-153 °C (after recrystallization from MeOH) ^{1}H-NMR δ 1 38 (t, J=7 1 Hz, 3H, OCH_2CH_3), 3 66 (d, J=0 5 Hz, 1H, H_5), 4 33 (q, J=7 1 Hz, 2H, OCH_2), 7 77 (dd, J=9 9 Hz, J=0 5 Hz, 1H, H_2), 8 04 (d, J=9 6 Hz, 1H, $H_{6'}$), 8 27 (d, J=9 9 Hz, 1H, H_1), 8 42 (dd, J=9 6 Hz, J=2 4 Hz, 1H, $H_{5'}$), 9 15 (d, J=2 4 Hz, 1H, $H_{3'}$), 11 42 (br s, 1H, N H), IR (KBr) ν 3600-3200 (N-H), 3300 (alkyne-H), 2100 (alkyne), 1700 (C=O), 1630 (C=C), 1350 cm^{-1}, EI/MS m/e 332 (M^+), 198, 122, 92, 78, Found C, 50 09, H, 3 62, N, 16 64 $C_{14}H_{12}O_6N_4$ requires C, 50 61, H, 3 64, N, 16 86

3-*Acetoxymethyl*-1 *(2,4 dinitrophenyl)hydrazino*-(E)-*pent*-2-*en*-4-*yne* **19c**

1 ml of a soln of 2,4 dinitrophenylhydrazine (0 25 g, 1 26 mmol) and H_2SO_4 (1 ml) in MeOH (20 ml) was added to a soln of **18c** (10 mg, 0 066 mmol) in MeOH (3 ml) to furnish[28] **19c** (4 mg, 18 %) as a red powder M p 143 °C (after recrystallization from MeOH) ^{1}H-NMR δ 2 17 (s, 3H, $COCH_3$), 3 55 (s, 1H, H_5), 4 71 (d, J=1 2 Hz, 2H, H_6), 6 77 (br d, J=9 6 Hz, 1H, H_2), 7 95 (d, J=9 6 Hz, 1H, H_6), 8 21 (d, J=9 6 Hz, 1H, H_1), 8 35 (dd, J=9 6 Hz, J=2 4 Hz, 1H, $H_{5'}$), 9 12 (d, J=2 4 Hz, 1H, $H_{3'}$), 11 23 (br s, 1H, N-H), IR (KBr) ν 3600 3200 (N-H), 3300 (alkyne-H), 1730 (C=O), 1330 cm^{-1}

Alkylation of **6a** *with MeLi*

To an ice-cooled soln of **6a** (100 mg, 0 62 mmol) was added MeLi (0 80 ml, 1 6 M soln in *n*-hexane, 1 28 mmol) in THF under N_2 using a syringe After stirring for 15 min the resulting soln was allowed to attain r t After stirring for another 15 min, NH_4Cl aq was added, and the mixture extracted (Et_2O), dried and concentrated to produce 95 mg of a mixture which consisted of **24a** and

25a in a ratio of 4 3 1 (70 % and 16 % crude yield, respectively)(Cap GC) Pure exo 4,5 *epoxy* exo-3-*methyl*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*en*-3-*ol* **24a** could be isolated by crystallization from EtOAc /*n*-hexane = 1/2 M p 98-101 °C ^{1}H-NMR δ 1 40 (s, 3H, C_3-CH_3), 1 22-1 50 (m, 2H, H_{10}), 1 56 (s, 1H), 2 51 (dd, J=7 2 Hz, J=4 2 Hz, 1H), 2 59-3 04 (m, 3H, H_1, H_2, H_6, H_7, OH), 3 07 (d, J=2 0 Hz, 1H, H_4 or H_5), 3 15 (d, J=2 Hz, 1H, H_4 or H_5), 6 08-6 22 (m, 1H, H_8 or H_9), 6 28 (dd, J=5 7 Hz, J=3 0 Hz, 1H, H_8 or H_9), IR (KBr) ν 3600-3200 (OH), 1135 cm^{-1}, EI/MS m/e 178 (M^+), 112 (M-C_5H_6), 95 (M-$C_5H_5^+$-H_2O), 66, Found 178 0995 $C_{11}H_{14}O_2$ requires 178 0994 The impure endo-4,5 *epoxy* exo-5-*methyl*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*en* exo-3-*ol* **25a** revealed the following spectral data ^{1}H-NMR δ 1 22 (s, 3H, C_5-CH_3), 1 18-1 73 (m, 3H, H_{10}, OH), 2 78-3 04 (m, 4H, H_1, H_2, H_6, H_7), 3 01 (s, 1H, H_4), 3 75 (d, J=2 7 Hz, 1H, H_3), 5 86 (dd, J=5 4 Hz, J=2 7 Hz, 1H, H_8 or H_9), 6 12 (dd, J=5 4 Hz, J=2 7 Hz, 1H, H_8 or H_9), IR (CCl_4) ν 3600-3100 (OH), 1255 cm^{-1}, CI/MS m/e 179 (M^++1), 161 (M+1-H_2O), 133, 113 (M+1-C_5H_6), 95 (M+1-C_5H_6-H_2O), 66, Found 179 1066 $C_{11}H_{15}O_2$ requires 179 1072

Exo-5-n-*butyl*-endo 4,5-*epoxy*-endo-*tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*en*-exo-3-*ol* **25b**

The same procedure as described for the methylation of **6a** was used, starting from **6a** (172 mg, 1 06 mmol) and *n* BuLi (1 33 ml, 2 13 mmol) to afford **25b** as a crude oil Flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1) gave **25b** (169 mg, 72 %) as a pure oil ^{1}H-NMR δ 0 79-1 04 (m, 3H, CH_3), 1 09-1 69 (m, 8H, H_{10}, C_5-$(CH_2)_3$), 2 31 (br s, 1H, OH), 2 78-3 09 (m, 4H, H_1, H_2, H_6, H_7), 3 00 (s, 1H, H_4), 3 71 (d, J=2 7 Hz, 1H, H_3), 5 84 (dd, J=5 7 Hz, J=2 7 Hz, 1H, H_8 or H_9), 6 16 (dd, J=5 4 Hz, J=2 7 Hz, 1H, H_8 or H_9), IR (CCl_4) ν 3600-3100 (OH), 1370, 1250 cm^{-1}, EI/MS m/e 220 (M^+), 203 (M+1-H_2O), 137 (M+1-C_5H_6-H_2O), Found 221 1536 (M+1) $C_{14}H_{21}O_2$ requires 221 1542

Exo-3-*acetoxy*-exo-5-n-*butyl* endo 4,5-*epoxy* endo *tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*ene* **26**

Stirring **25b** (140 mg, 0 636 mmol) and 4-dimethylaminopyridine (DMAP) (8 mg, 0 066 mmol) in an excess of Ac_2O/pyridine for 90 min at r t gave **26** (162 mg, 97 %, 95 % pur Cap GC) as a white solid M p 84-93 °C (after recrystallization from *n*-hexane) ^{1}H-NMR δ 1 00-1 86 (m, 11H, C_5-$(CH_2)_3CH_3$, H_{10}), 1 98 (s, 3H, $COCH_3$), 2 19 (s, 1H, H_6), 2 70-2 93 (m, 3H, H_1, H_2, H_7), 3 00 (s, 1H, H_4), 4 42 (d, J=2 8 Hz, 1H, H_3), 5 86 (dd, J=5 4 Hz, J=2 7 Hz, 1H, H_8 or H_9), 6 09 (dd, J=5 4 Hz, J=2 7 Hz, 1H, H_8 or H_9), IR (CCl_4) ν 1735 (C=O), 1370, 1240 cm^{-1}

Exo-3-n *butyl* endo *tricyclo*[5 2 1 $0^{2,6}$]*dec*-8-*en*-endo-3-exo-5-*diol* **27**

$LiAlH_4$ (200 mg, 5 27 mmol) was suspended in Et_2O (20 ml) followed by addition of a soln of **26** (100 mg, 0 38 mmol) in Et_2O (10 ml) After 30 min stirring at r t the resulting mixture was cooled to -78 °C and hydrolyzed successively with water and 3 % HCl aq After extraction (Et_2O), drying and evaporation *in vacuo*, **27** (76 mg, 90 %) was obtained as a white solid M p 109-111 °C (after recrystallization from Et_2O) ^{1}H-NMR δ 1 09-1 70 (m, 12H, H_{10}, C_3-$(CH_2)_3CH_3$, OH), 1 58 (d, J=1 4 Hz, 1H, H_2), 1 77 A of AB (d, J=3 4 Hz, 1H, H_4), 1 81 B of AB (d, J=3 4 Hz, 1H, H_4), 2 60-2 75 (br s, 1H,

OH), 2.70 (d, J=2.9 Hz, 1H, H_6), 2.73-3.04 (m, 2H, H_1, H_7), 3.73 (dt, J=5.3 Hz, J=2.9 Hz, 1H, H_5), 6.09 (dd, J=5.7 Hz, J=2.5 Hz, 1H, H_8 or H_9), 6.31 (dd, J=5.7 Hz, J=2.5 Hz, 1H, H_8 or H_9); IR (KBr): ν 3600-3000 (OH), 1145 cm^{-1}; EI/MS: m/e 205 ($M+1-H_2O$), 165 ($M-C_4H_9^+$), 147 ($M-C_4H_9^+-H_2O$), 129 ($M-C_4H_9^+-2H_2O$), 99, 66; Found C, 75.24; H, 10.02. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97.

Acid-catalyzed cyclization of **8b**

Alcohol **8b** (130 mg, 0.55 mmol) and *p*-toluenesulfonic acid (40 mg, 0.26 mmol) were dissolved in $CHCl_3$ (8 ml) and heated at reflux for 90 min. After cooling to r.t., H_2O was added and the resulting mixture was extracted with Et_2O (3x), washed, dried and evaporated *in vacuo* to yield a crude mixture (170 mg) which contained **33** and an isomer in molar ratio 3:1 (Cap GC). After flash chromatography an oil (110 mg) was obtained which contained 70 % of *ethyl 2-hydroxy-9-oxapentacyclo*-[6.3.0.$0^{3,7}$.$0^{4,11}$.$0^{6,10}$]*undecane 3-carboxylate* **33**. ^{1}H-NMR: δ 1.27 (t, J=7 Hz, 3H, CH_3), 1.46 A of AB (d, J=10 Hz, 1H, H_5), 1.71 B of AB (d, J=10 Hz, 1H, H_5), 2.11-3.06 (m, 6H, H_1, H_4, H_6, H_7, H_{11}, OH), 4.18 (q, J=7 Hz, 2H, OCH_2), 4.40 (d, J=2 Hz, 1H, H_2), 4.49-4.64 (m, 1H, H_8 or H_{10}), 4.93-5.11 (m, 1H, H_8 or H_{10}); IR (CCl_4): ν 3600-3300 (OH), 2980, 1730-1710 (C=O) cm^{-1}; CapGC/EI/MS: m/e 236 (M^+), 218 ($M-H_2O$), 191 ($M-C_2H_5O^+$), 162 (M-HOEt-CO), 138.

Ethyl 2-acetoxy-9-oxapentacyclo[6.3.0.$0^{3,7}$.$0^{4,11}$.$0^{6,10}$]*undecane 3-carboxylate* **34**

The crude **33** (106 mg, 0.45 mmol) obtained above, was reacted with an excess of Ac_2O/pyridine following the usual procedure, to produce a crude mixture which mainly consisted of **34** (Cap GC). After flash chromatography (silica gel, EtOAc /*n*-hexane = 1/1, I_2, Rf = 0.4) and crystallization from *n*-hexane, analytically pure **34** (45 mg, 36 %) was obtained. M.p. 72-74 °C. ^{1}H-NMR (90 MHz): δ 1.24 (t, J=7.1 Hz, 3H, CH_3), 1.53 (br s, 2H, H_5), 2.04 (s, 3H, $COCH_3$), 2.16-2.55 (m, 3H), 2.58-2.89 (m, 2H, H_1, H_4, H_6, H_7, H_{11}), 4.14 (q, J=7.1 Hz, 2H, OCH_2), 4.49-4.64 (m, 1H, H_8 or H_{10}), 4.80-4.96 (m, 1H, H_8 or H_{10}), 5.36 (d, J=2.0 Hz, 1H, H_2); ^{1}H-NMR (400 MHz): δ 1.24 (t, J=7.2 Hz, 3H, CH_3), 1.51 A of AB (br d, ^{2}J=11.5 Hz, 1H, H_5), 1.55 B of AB (br d, ^{2}J=11.5 Hz, 1H, H_5), 2.05 (s, 3H, $COCH_3$), 2.29 (q, J=5.8 Hz, 1H), 2.40-2.43 (m, J≅3 Hz (fine splittings), 1H), 2.45-2.48 (m, 1H), 2.66 (dquint, J=5.8 Hz, J=1.6 Hz, 1H), 2.79 (td, J=5.7 Hz, J=1.1 Hz, 1H, H_1, H_4, H_6, H_7, H_{11}), 4.14;4.15 (q;q, J=7.2 Hz, 2H, diastereotopic CH_2), 4.56-4.59 (m, 1H, H_8 or H_{10}), 4.90 (td, J=3.5 Hz, J=1.5 Hz, 1H, H_8 or H_{10}), 5.35 (d, J=2.3 Hz, 1H, H_2); IR (KBr): ν 3000, 1760, 1737, 1720 (C=O), 1285, 1230, 1085, 960 cm^{-1}; EI/MS: m/e 278 (M^+), 236 ($M-C_2H_2O^+$), 218 ($M-CH_3COOH$), 43 (CH_3CO^+); Found C, 64.36; H, 6.55. $C_{15}H_{18}O_5$ requires C, 64.74; H, 6.52.

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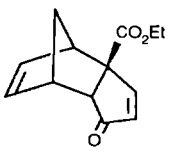
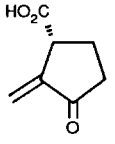
SUMMARY

This thesis deals with the use of *endo*-tricyclo[5 2 1 $0^{2,6}$]decadienone ester **1** as a synthon for cyclopentenoids with an exo-cyclic enone function, *e g* sarkomycin **2** In the introductory Chapter the synthesis and reactions of tricyclo[5 2 1 $0^{2,6}$]decadienones **3** are briefly reviewed in connection with their use as synthons for cyclopentenones **4**, with defined stereochemistry and chirality



1



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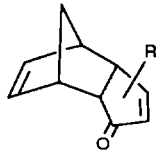

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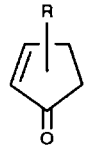
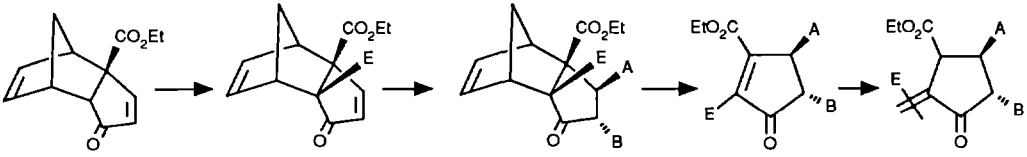


4

The synthetic concept underlying the preparation of cyclopentenoids with an exo-cyclic double bond is presented in Scheme 1

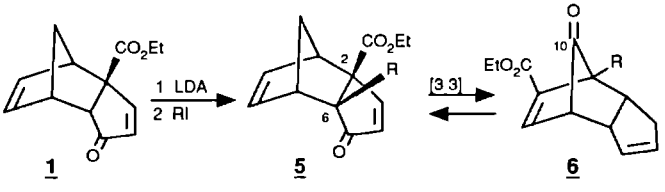
Scheme 1



1

In Chapter 2 the angular alkylation of **1** with alkyl halides is described A considerable diminished thermal stability was encountered in the angularly alkylated products **5** (Scheme 2) Tricyclic compounds **5** were shown to undergo a Cope rearrangement to **6** at ambient temperature The equilibrium between **5** and **6** can be explained in terms of a greater steric interaction between the group R and the 2-ethoxycarbonyl function in **5** The presence of the 6 alkyl group in **5** has a notable influence on their

Scheme 2

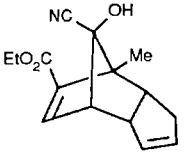


1 **5** **6**

R-Me Et allyl n heptyl

aptitude to undergo conjugate nucleophilic addition In some cases (*e g* cyanide addition), **5** (R=Me) itself does not react with cyanide Instead, after Cope rearrangement to **6**, stereoselective addition at the C_{10} keto group leads to the *syn*-cyanide **7** The decreased skeletal stability of **5** also leads to a facile [4+2] cycloreversion in DMF at 150 °C to give the intermediate cyclopentadienone carboxylates

8, which either dimerize or react with the liberated cyclopentadiene The intermediacy of free **8** was proven by performing a crossed Diels Alder reaction with an excess of cyclopentadiene to afford esters **9** in high yields



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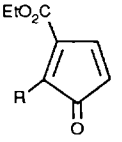
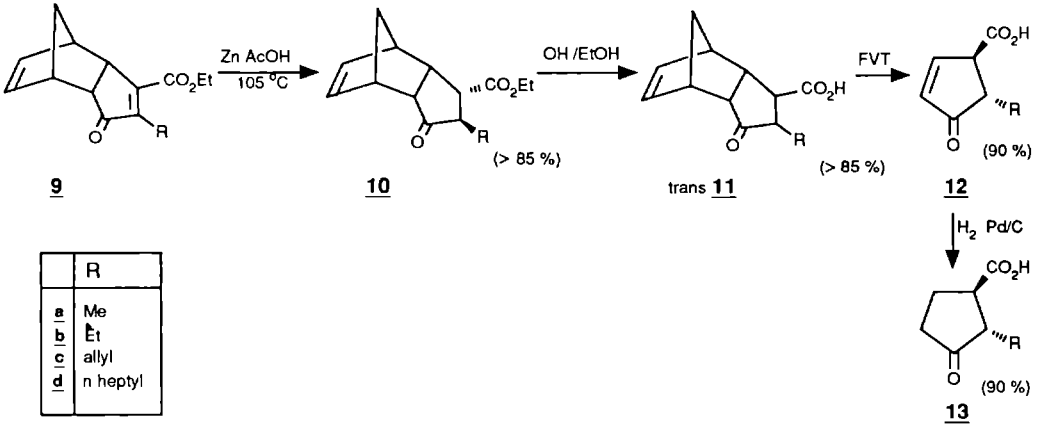


8

R Me Et allyl n heptyl benzyl

Regio- and stereoselective reduction of **9** with Zn/AcOH afforded *trans*-esters **10** (Scheme 3), which were hydrolyzed to *trans*-carboxylic acids **11** Subsequent Flash Vacuum Thermolysis (FVT) gave cyclopentenones **12** Reduction of the enone olefinic moiety completes the synthesis of dihydrosarkomycins **13** In the appendix of this Chapter the FVT apparatus and its experimental use are described

Scheme 3



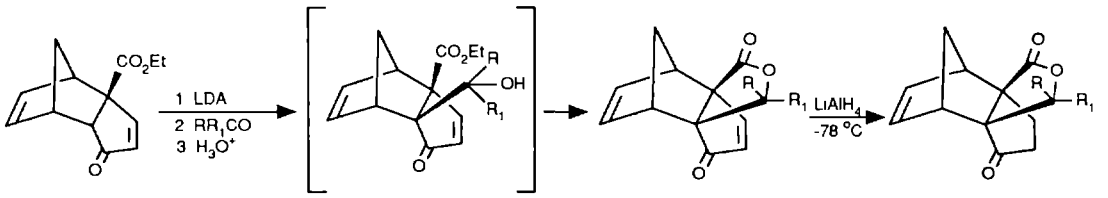
9 **10** trans **11** **12** **13**

	R
a	Me
b	Et
c	allyl
d	n heptyl

Chapter 3 deals with the angular condensation of ester **1** with various aldehydes and ketones It was shown that in nearly all studied cases [4 3 3]oxapropellanes **15** were isolated (Scheme 4) Only in the case of $R=R_1=H$ a mixture of the intermediate carbinol **14** and lactone **15** was formed The formation of tetracyclic lactones **15** appeared to be a highly stereoselective process when bulky aldehydes were used It was shown that the condensation/lactonization with benzaldehyde proceeded with opposite stereochemistry in comparison with the addition of pivalaldehyde This different stereochemistry was tentatively rationalized by considering the respective transition states

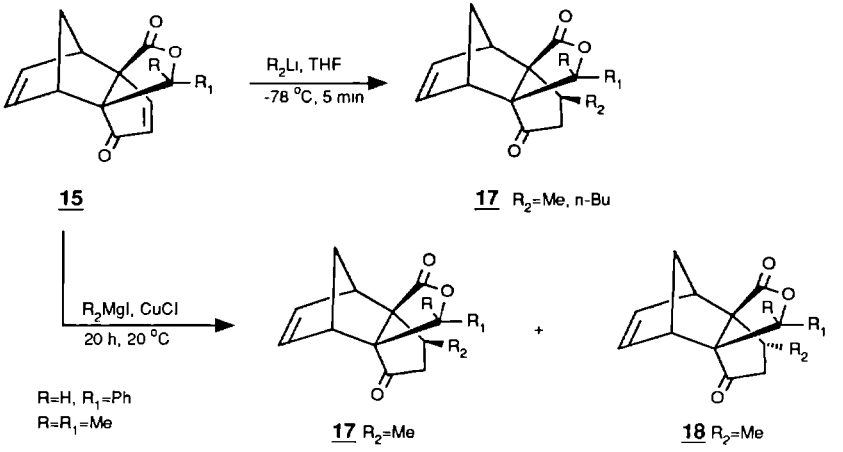
The [4 3 3]oxapropellanes **15** are prone to undergo conjugate nucleophilic addition reactions Reduction of **15** with $LiAlH_4$ gave the lactones **16** in high yields Neither 1,2-addition nor opening of the lactone moiety was observed This can be explained by steric shielding of both carbonyl groups in **15**

Scheme 4



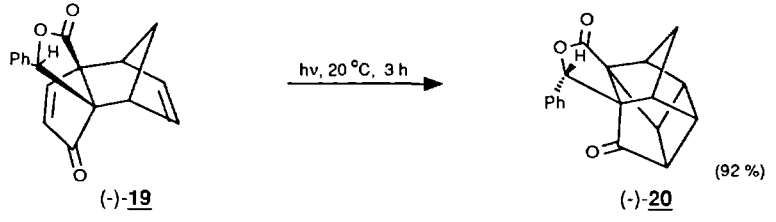
Reaction of **15** with organometallic reagents, such as MeMgI/ Cu(I)Cl or RLi, gave similar results. The stereochemistry of the alkyllithium addition differed from the Cu(I)-catalyzed Grignard addition. In the first-mentioned case only *anti*-addition with respect to the norbornene moiety of **15**, to give **17**, was observed (Scheme 5), whereas with the last-mentioned reagent also *syn*-addition to the enone moiety of **15**, to give **18**, occurred. This result was explained by d-orbital stereoelectronic control in the organocopper complex formed.

Scheme 5



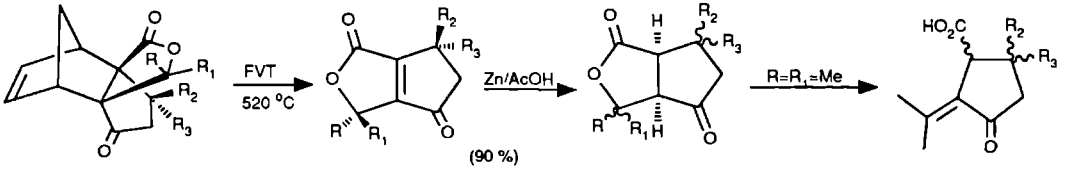
Irradiation of optically active (-)-**19** (*vide infra*) gave the annelated optically active bishomocubanone (-)-**20** in a yield of 92 % (Scheme 6).

Scheme 6



In Chapter 4, the FVT of the lactones **16**-**18** is described. During this thermolysis the cyclopentenoid butenolides **21** were formed in high yields (Scheme 7). These bicyclic structures **21** were regio and stereoselectively reduced with Zn in AcOH to afford the cyclosarkomycins **22** in moderate to high yields. The reaction temperature is a crucial parameter in this reduction The stereochemical course of this zinc reduction strongly depends on the substituents R, R_1, R_2 and R_3. When higher temperatures were applied in the Zn/AcOH reduction of lactones **16**-**18**, mixtures of cyclosarkomycins **22** and sarkomycins **23** were formed for R=R_1=Me. The formation of **23** is explained by an eliminative lactone opening of **22**.

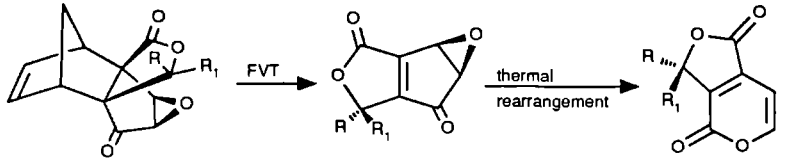
Scheme 7



16-**18** **21** **22** **23**

The thermal conversion of epoxides **24**, using FVT at 450 °C, gave mixtures of annelated cyclopentadienone oxides **25** and pyrones **26** (Scheme 8). FVT at more elevated temperatures gave pyrones **26** in yields of *ca.* 50 %.

Scheme 8

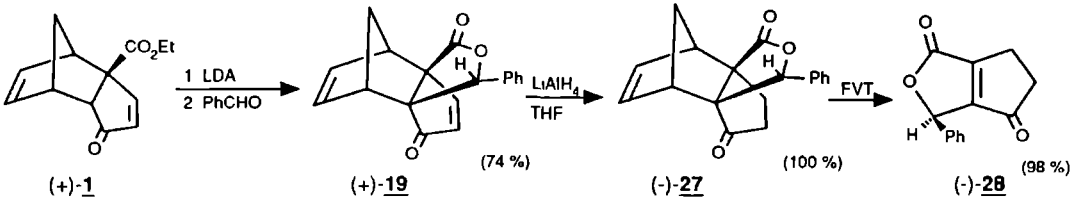


24 **25** **26**

	R	R_1
a	H	H
b	H	Ph
c	t-Bu	H
d	n hexyl	H
e	-$(CH_2)_5$	
f	Me	Me

Chapter 5 deals with the synthesis of optically pure cyclopentenoid butenolides **28** Optically pure ester (+)-**1** was converted into lactone (+)-**19** (Scheme 9). Subsequent conjugate reduction with

Scheme 9



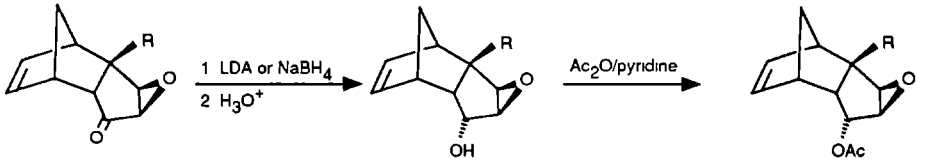
(+)-**1** (+)-**19** (-)-**27** (-)-**28**

$LiAlH_4$ gave optically pure (-)-**27** Finally, FVT furnished optically pure (-)-**28**. The optically pure antipodes (-)-**19**, (+)-**27** and (+)-**28** were similarly prepared The close agreement of the optical rota-

tions for all antipodes proves the conservation of optical integrity during the reaction sequence used.

In Chapter 6, reactions of epoxytricyclodecenones **29** with bases are described. Reaction of **29** with LDA did not result in angular deprotonation but unexpectedly afforded *endo*-alcohol **30** (Scheme 10). This stereoselective formation of **30** was explained by assuming a β-hydride transfer from LDA to the keto function of **29**.

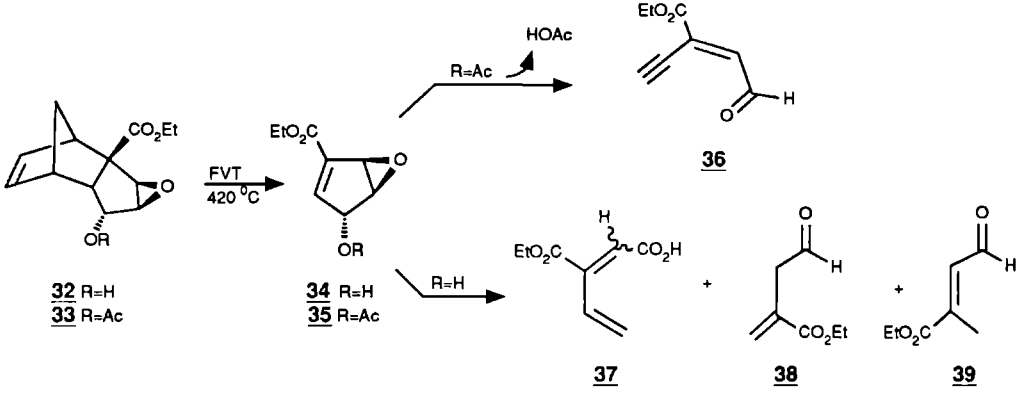
Scheme 10



29 R=H, CO_2Et **30** **31**

The thermal cycloreversion of *endo*-alcohols **30** and their acetates **31** was compared with that of ketones **29**. FVT of **32** at 420 °C afforded cyclopentadiene oxide **34** in 47 % yield (Scheme 11).

Scheme 11

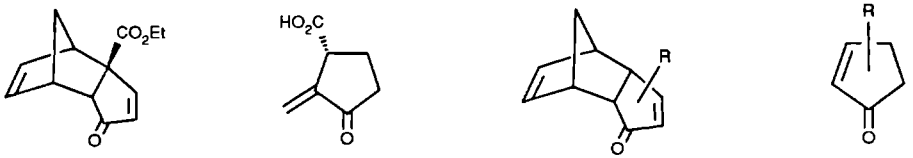


The corresponding acetate **33** similarly gave **35**. However, the parent cyclopentene epoxides of **34** and **35** could not be obtained. At more elevated temperatures (525 °C) the intermediate epoxide **35** undergoes a further rearrangement to pent-2-en-4-ynal **36**. At thermolysis temperatures of ≥ 480 °C, carbinol **34** was converted into a mixture of butadiene carboxylic acids **37** and the aldehydes **38** and **39**. A mechanistic explanation for the respective formation of compounds **36**-**39** is presented. Finally, intramolecular epoxide opening reactions of **30** (R=H) and some of its 3-alkyl derivatives were studied.

A summary in English and Dutch concludes this thesis.

SAMENVATTING

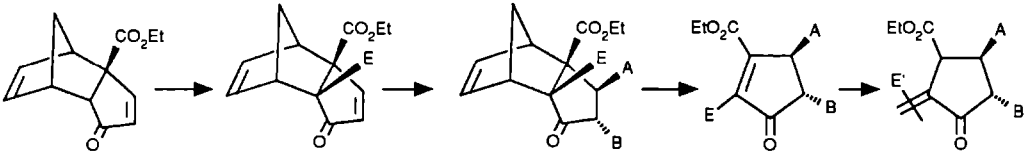
Dit proefschrift handelt over het gebruik van *endo*-tricyclo[5.2.1.$0^{2,6}$]decadiënon **1** als synthon voor cyclopentenonen die een exo-cyclische enonfunctie bevatten, zoals sarkomycine **2**. In het inleidende hoofdstuk wordt een kort overzicht gegeven van de synthese en eigenschappen van tricyclo[5.2.1.$0^{2,6}$]decadiënonen **3** in samenhang met hun gebruik als synthonen voor cyclopentenonen **4**, met vastgelegde stereochemie en chiraliteit.



1 **2** **3** **4**

Het synthetisch concept dat ten grondslag ligt aan de synthese van cyclopentenoïden met een exo-cyclische dubbele binding is weergegeven in Schema 1.

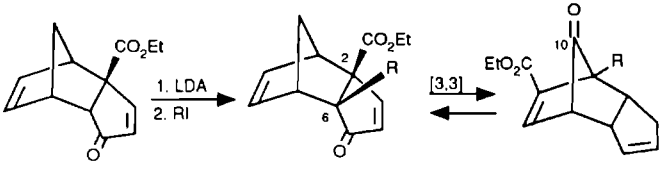
Schema 1



1

In Hoofdstuk 2 wordt de angulaire alkylering van **1** met alkylhalides beschreven. Bij de gealkyleerde produkten **5** wordt een sterk verminderde thermische stabiliteit waargenomen (Schema 2). Reeds bij kamertemperatuur ondergaan deze verbindingen een Cope omlegging tot de ketonen **6**. Hierbij is zowel de snelheid van omlegging als de ligging van het evenwicht tussen **5** en **6** afhankelijk van de grootte van R. Dit resultaat kan worden verklaard door de grotere sterische interactie tussen de groep R en de 2-ethoxycarbonyl substituent in **5**. De aanwezigheid van de 6-alkylgroep in **5** heeft een aan-

Schema 2

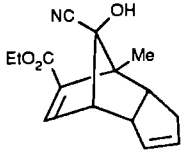


1 **5** **6**

R=Me, Et, allyl, n-heptyl

zienlijke invloed op hun vermogen om geconjugeerde nucleofiele addities te ondergaan. Het blijkt in sommige gevallen (b.v. cyanide additie) dat **5** (R=Me) niet zelf met het cyanide reageert. In plaats daarvan legt **5** eerst om tot **6**, waarna stereoselectieve additie van CN^- aan de C_{10}-keto funktie van **6**

tot het *syn*-cyanide **7** leidt De afgenomen stabiliteit van **5** geeft aanleiding tot een snelle [4+2] cyclo reversie in DMF bij 150 °C tot de intermediaire cyclopentadienon esters **8**, die vervolgens dimeriseren of reageren met het vrijgekomen cyclopentadieen De vorming van **8** is aangetoond door een gekruiste Diels-Alder reactie uit te voeren met een overmaat cyclopentadieen Hierbij worden de esters **9** in hoge opbrengsten gevormd



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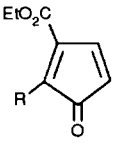
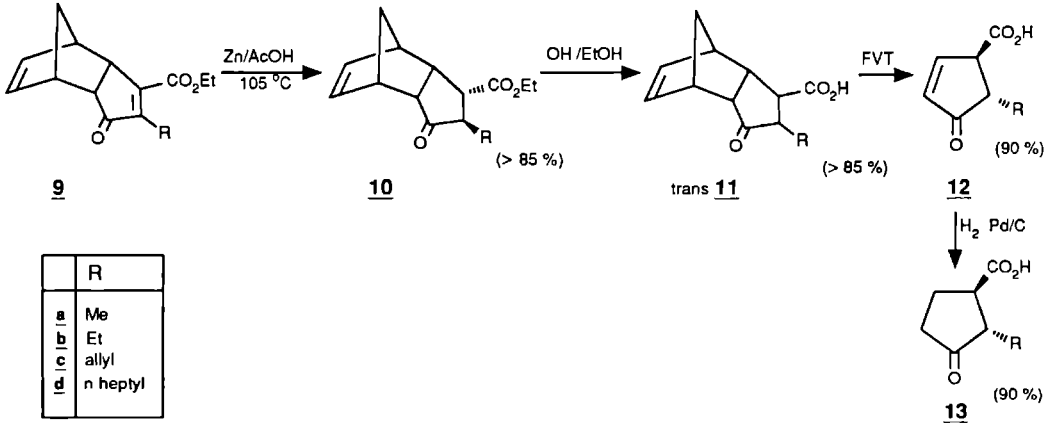


8

R=Me Et allyl n heptyl benzyl

Regio- and stereoselectieve reductie van **9** met zink in azijnzuur geeft de *trans*-esters **10** (Schema 3), die vervolgens worden gehydrolyseerd tot de *trans*-carbonzuren **11** Flits Vacuum Thermolyse (FVT) levert de cyclopentenonen **12** Katalytische reduktie van de olefinische binding met waterstof completeert de synthese van de dihydrosarkomycines **13** In de appendix van dit hoofdstuk wordt de FVT apparatuur en de gevolgde experimentele procedure beschreven

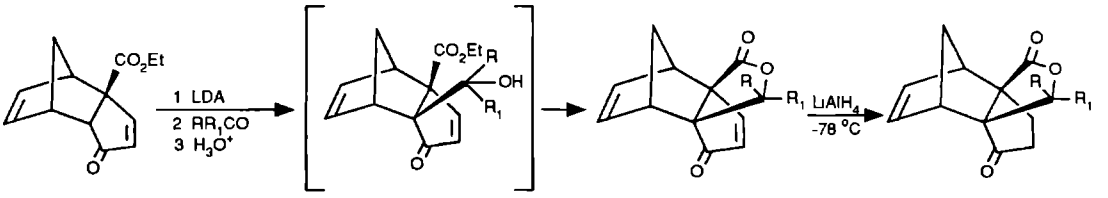
Schema 3



	R
a	Me
b	Et
c	allyl
d	n heptyl

Hoofdstuk 3 handelt over de angulaire condensatie van ester **1** met een aantal aldehyden en ketonen In bijna alle bestudeerde gevallen worden de gevormde [4 3 3]oxapropellanen **15** meteen geïsoleerd (Schema 4) Alleen als $R=R_1=H$ wordt een mengsel van het intermediaire carbinol **14** en lacton **15** gevormd De vorming van de tetracyclische lactonen **15** blijkt stereoselectief te verlopen als sterisch gevulde aldehyden worden gebruikt Er is aangetoond dat de condensatie/lactonisatie van benzaldehyde stereochemisch omgekeerd verloopt ten opzichte van pivalaldehyde Dit verschil in stereo selectiviteit is verklaard door een beschouwing van de respectievelijke overgangstoestanden De

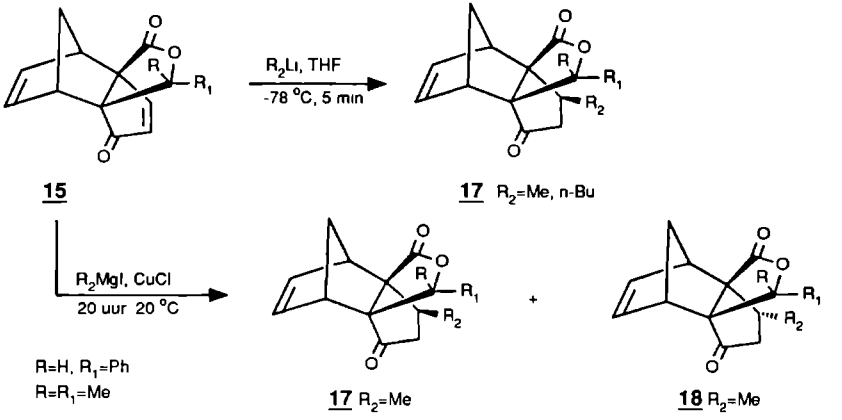
Schema 4



1 **14** **15** **16**

[4.3.3]oxapropellanen **15** ondergaan gemakkelijk geconjugeerde nucleofiele addities. Reductie van **15** met $LiAlH_4$ geeft de lactonen **16** in hoge opbrengsten. Hierbij wordt noch 1,2-additie, noch opening van de lactonring waargenomen. Dit kan worden verklaard door sterische afscherming van beide carbonylgroepen in **15**. Reactie van **15** met organometaalverbindingen, zoals MeMgI/Cu(I)Cl of RLi, geeft analoge resultaten. De stereochemie van de alkyllithium-additie verschilt van de Cu(I)-gekatalyseerde Grignard-reaktie. In het eerstgenoemde geval wordt alleen *anti*-additie ten opzichte van het norborneengedeelte van **15** gevonden, waarbij in hoge opbrengsten verbindingen **17** worden gevormd (Schema 5). In het laatstgenoemde geval blijkt daarnaast ook *syn*-additie aan de enongroep van **15** te hebben plaatsgevonden, waarbij zich **18** vormt. Dit afwijkende resultaat wijst op stereoelectronische interakties door d-orbitalen in het gevormde organokoper complex.

Schema 5



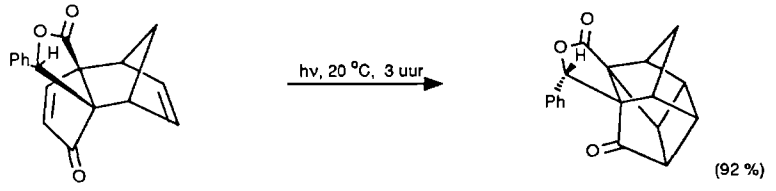
15 **17** R_2=Me, n-Bu

17 R_2=Me **18** R_2=Me

Bestraling van optisch actief (-)-**19** (*vide infra*) geeft het geanneleerde optisch aktieve bishomocubanon (-)-**20** in 92 % opbrengst (Schema 6).

In Hoofdstuk 4 wordt de FVT van de lactonen **16**-**18** beschreven. Hierbij vormen zich de cyclopentenoïde butenolides **21** in hoge opbrengsten (Schema 7). Deze bicycli **21** kunnen regio- en stereoselectief worden gereduceerd met zink in azijnzuur tot de cyclosarkomycines **22** in redelijke tot hoge opbrengsten. De reaktie temperatuur is hierbij van cruciaal belang. Het stereochemisch verloop van

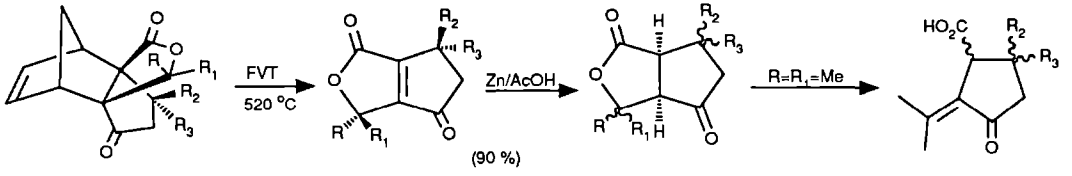
Schema 6



(-)-**19** (-)-**20**

deze zinkreduktie blijkt sterk afhankelijk te zijn van de substituenten R, R_1, R_2 en R_3. Wanneer de Zn/AcOH redukties worden uitgevoerd bij een hogere temperatuur ontstaan er, als $R=R_1$=Me, mengsels van **22** en de sarkomycines **23**. De vorming van **23** kan worden verklaard door eliminatieve opening van de lactonring van **22**.

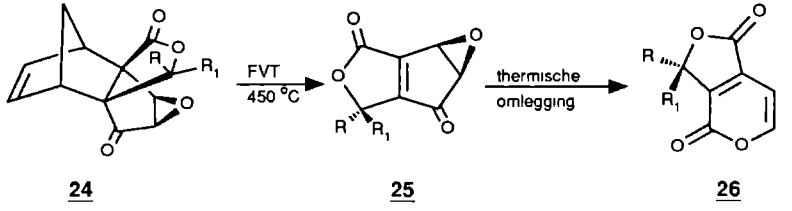
Schema 7



16-18 **21** **22** **23**

De thermische omzetting van de epoxides **24** met behulp van FVT bij 450 °C leidt tot mengsels van de geanneleerde cyclopentadiënon oxides **25** en de pyronen **26** (Schema 8). FVT bij hogere temperaturen levert uitsluitend de pyronen **26** in *ca.* 50 % opbrengst.

Schema 8



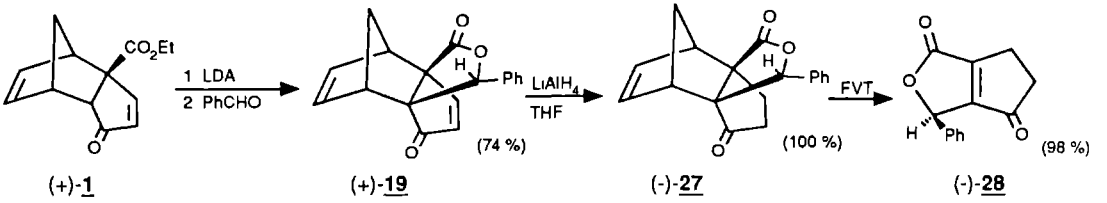
24 **25** **26**

	R	R_1
a	H	H
b	H	Ph
c	t-Bu	H
d	n-hexyl	H
e	$-(CH_2)_5-$	
f	Me	Me

Hoofdstuk 5 handelt over de synthese van optisch zuivere cyclopentenoïde butenolides **28**. Hiertoe is optisch zuivere ester (+)-**1** omgezet in lacton (+)-**19** (Schema 9). Een daaropvolgende geconjugeerde reductie met $LiAlH_4$ leidt tot optisch zuiver (-)-**27**. Tenslotte wordt, door toepassing van FVT, optisch zuiver (-)-**28** verkregen. De optisch zuivere antipoden (-)-**19**, (+)-**27** en (+)-**28** zijn op overeenkomstige wijze bereid. De goede overeenkomst tussen de optische draaiingen voor alle antipoden vormen onder meer een bewijs voor het behoud van de optische integriteit tijdens de gebruikte routes.

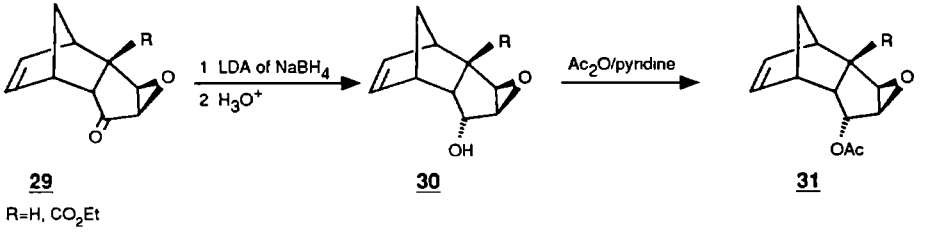
In Hoofdstuk 6 worden reacties van epoxytricyclodecenonen **29** met basen beschreven. Reaktie van

Schema 9



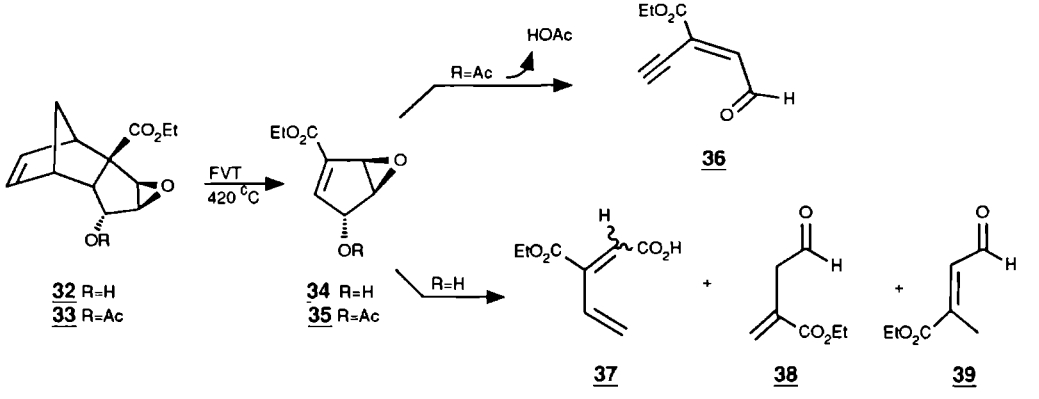
29 met LDA laat niet de verwachte angulaire deprotonering zien, doch leidt tot de vorming van *endo*-alcohol 30 (Schema 10). De stereoselectieve vorming van 30 kan worden verklaard door een β-hydride overdracht vanuit het LDA naar de keto functie van 29.

Schema 10



De thermische cycloreversie van de *endo*-alcoholen 30 en hun acetaten 31 is vergeleken met die van de ketonen 29. FVT van 32 bij 420 °C levert de cyclopentadieen-oxiden 34 in 47 % opbrengst (Schema 11).

Schema 11



Op analoge wijze wordt 35 verkregen uit het overeenkomstig acetaat 33. De aanwezigheid van de carboalkoxy groep is essentieel daar zowel alcohol 30 (R=H) als diens acetaat 31 (R=H) geen cyclopentadieen oxides opleveren bij cycloreversie. Bij de toepassing van hogere oven temperaturen (525

°C) legt het intermediaire epoxide **35** thermisch verder om tot pent-2-en-4-ynal **36**. Het carbinol **32** wordt bij hogere temperaturen (≥ 480 °C) omgezet in een mengsel van butadieencarbonzuren **37** en de aldehydes **38** en **39**. Een mechanistische verklaring voor de respectieve vorming van **36**-**39** wordt voorgesteld. Tenslotte worden intramoleculaire epoxide-openingen van **30** (R=H) en enkele van haar 3-alkyl derivaten beschreven.

Een Nederlandse en Engelse samenvatting besluiten dit proefschrift.

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CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 29 maart 1959 te Mill en Sint Hubert. Op 17 juni 1977 behaalde hij het diploma Atheneum-B aan het Elzendaalcollege te Boxmeer. In hetzelfde jaar werd begonnen met de studie scheikunde aan de Katholieke Universiteit te Nijmegen. Het kandidaatsexamen (S_2) werd afgelegd op 24 november 1980. De doctoraalstudie bevatte als hoofdrichting Organische Chemie (Prof. Dr. R.J.F. Nivard, Dr. J.W. Scheeren, onderwerp: cycloaddities van α,β-gefunctionaliseerde aldehydes aan 1,1-dimethoxypropeen), een bijvak Toxicologie (Prof. Dr. P.Th. Henderson, onderwerp: isolatie en karakterisering van polaire mutagene verbindingen in creosoot P1) en een bijvak Analytische Chemie (Prof. Drs. G. Kateman, onderwerp: de toepassing van simplex optimalisatie bij atomaire absorptie spektrometrie). Het doctoraalexamen werd behaald op 28 mei 1984.

Vanaf 1 juni 1984 tot en met 31 mei 1988 was hij in dienst als wetenschappelijk medewerker aan het laboratorium voor Organische Chemie van de Katholieke Universiteit te Nijmegen. In deze periode werd onder leiding van Prof. Dr. B. Zwanenburg en Dr. A.J.H. Klunder, op een project van de stichting Scheikundig Onderzoek in Nederland (SON), het in dit proefschrift beschreven onderzoek verricht.

Gedurende zijn studie en promotieonderzoek was hij als assistent betrokken bij het onderwijs aan studenten in de vakken Organische Chemie en Chemie & Samenleving.

Sinds 1 september 1988 is hij werkzaam bij Duphar B.V. te Weesp.